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TUBERCLE BACILLI IN LATENT TUBERCULOUS LESIONS AND IN LUNG TISSUE WITHOUT TUBERCULOUS LESIONS *

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Anatomic study demonstrates that the bodies of children, with increasing frequency as age progresses, and the bodies of almost all adults contain lesions with characteristics indicating that they are tuberculous in origin. Many of the lesions apparently are completely healed. Since they furnish evidence of past infection, it is desirable to determine whether they contain living tubercle bacilli and are a possible source of dissemination.

These lesions of tuberculosis fall into two important groups: (*a*) a childhood type, situated in any part of the lung and associated with corresponding lesions in adjacent lymph nodes; (*b*) an adult type, having its origin in the apex of the lung and unaccompanied by tuberculosis of lymph nodes. In order to determine whether the adult type of disease has its origin in the focal lesions of childhood, it is desirable to know whether the focal lesions contain living tubercle bacilli at the time when the lesion of adult type makes its appearance.

Numerous observations show that material from calcified nodules injected into guinea-pigs produces tuberculosis. Rabinowitsch [1] found living tubercle bacilli in nearly one half of these calcified lesions and in nearly two thirds of the softer nodules with chalklike contents. Similar observations have been made by Lubarsch,[2] Schmitz,[3] Wegelin [4] and many others.

A discrepancy between anatomic and bacteriologic criteria of latent infection is introduced by well known observations which show that normal lymph nodes of children often contain living tubercle bacilli

* From the Henry Phipps Institute, University of Pennsylvania.

1. Rabinowitsch, L.: Arb. a. d. path. Inst. zu Berlin, Festschr. f. Orth, 1906, p. 365; Ztschr. f. Tuberk. **15**:217, 1909.
2. Lubarsch, O.: Deutsche med. Wchnschr. **34**:1921, 1908.
3. Schmitz, E.: Frankfürt. Ztschr. f. Path. **3**:88, 1909.
4. Wegelin, C.: Cor.-Bl. f. schweiz. Aerzte **40**:913, 1910.

capable of producing tuberculosis in small animals. Loomis,[5] in 1891, found living tubercle bacilli in lymph nodes which did not exhibit gross evidence of tuberculosis. Similar studies controlled by histologic examination have been made by Kälble,[6] Macfadyen and MacConkey,[7] Harbitz,[8] Weber and Baginsky[9] and others. In preparing the description of examples of his own several years ago, Wang[10] found in the literature of the subject record of 357 instances in which normal lymph nodes were examined by inoculation of guinea-pigs to determine whether tubercle bacilli were present and they were found in 12 per cent.

The present study has been aided during two years, namely 1924 and 1925, by generous appropriations from the National Tuberculosis Association. The lungs examined were obtained from the Philadelphia General Hospital through Dr. E. B. Krumbhaar and from the Pennsylvania Hospital through Dr. John R. Paul.

We have examined approximately 304 lesions obtained from the lungs of 169 persons (tables 1 and 5). We have inoculated into guinea-pigs material from a considerable number of each type of latent lesion and have repeatedly examined lesions of different types which occurred in the same lungs. Focal lesions were classified as caseous, caseous encapsulated, caseous calcified and calcified. Lesions of lungs and of tracheobronchial lymph nodes were classified separately. Apical lesions were listed as (*a*) fibrous scars of the pleura, when the pleura and a thin layer of underlying tissue was implicated in the lesion; (*b*) fibrous scars of the apex; (*c*) fibrocaseous tuberculosis of the apex; (*d*) fibrocaseous and calcified tuberculosis of the apex; (*e*) fibrous and calcified scars of the apex.

The surface of the lung or lymph node to be examined was seared, and a piece of tissue from 1 to 2 cm. across was removed with sterile instruments. The tissue was scraped with a knife unless calcified, and ground in a sterilized mortar with from 2 to 3 cc. of salt solution. Of the suspension obtained, 1 cc. was injected into the subcutaneous tissue in the inguinal region of each of two guinea-pigs. When the guinea-pigs became tuberculous, cultures were obtained in all but two instances (table 1, 104 *A* and 146 *A*).

In table 1 are collected, with as much brevity as possible, essential data concerning each one of the latent lesions from which material was injected into guinea-pigs. The autopsy number is that assigned by us. The race, namely, white or colored, sex and age are cited, in order to

5. Loomis, H. P.: M. Rec. **38**:689, 1890.
6. Kälble, J.: München. med. Wchnschr. **46**:622, 1899.
7. Macfadyen, A., and MacConkey, A.: Brit. M. J. **2**:129, 1903.
8. Harbitz, F.: J. Infect. Dis. **2**:143, 1905.
9. Weber, A., and Baginsky, A.: Tuberk. Arb. a. d. k. Gsndhtsamte. **7**:102, 1907.
10. Wang, C. Y.: Lancet **2**:417, 1916.

determine whether these factors materially affected the incidence of living tubercle bacilli in the tissues.

The lesions tested in guinea-pigs were obtained from persons who died from diseases other than tuberculosis, and the table shows the cause of death in each instance. Tuberculosis was regarded as latent when it was unaccompanied by symptoms or physical signs recognized by the physician. The distinction between latent and manifest disease is obviously artificial and every transition from one to the other may be found. The table shows how frequently those who died from causes other than tuberculosis harbored living tubercle bacilli.

In table 1, under "lesions of the lung," are listed those lesions which are presumably the result of tuberculous infection. When caseation has been present a diagnosis of tuberculosis can be made, and with calcification it is almost invariably evident that a caseous tuberculous lesion has undergone calcification. Fibrous scars of the apical pleura do not have any characteristics which serve to show that the lesion was tuberculous in origin, and it is possible that they may be produced by other causes. Fibrous scars of the apex, consisting of wedges or irregularly shaped strands of fibrous tissue penetrating from the pleura a variable distance within the lung substance, were examined histologically in all instances, and in none of them were the characteristics of tuberculosis recognized. Nevertheless, not infrequently, an apical scar is found on one side and fibrocaseous tuberculosis on the other; furthermore, it will be shown that a considerable part of these fibrous scars, namely, one-fourth, contain living tubercle bacilli. Fibrocaseous lesions of the apex contained living tubercle bacilli in three fourths of the instances in which examination was made. It is not improbable that tubercle bacilli may be disseminated from one of these apical lesions, or perhaps from focal tuberculous lesions to other parts of the lung. For this reason, associated lesions of the lung present in each autopsy are listed in table 1.

Material from each lesion tested was inoculated into two guinea-pigs, but in some instances one animal died so soon, usually from acute bacterial infection that tuberculosis was not afforded an opportunity for development (approximately three weeks), and in these instances only one animal is listed in the table. Occasionally one animal developed tuberculosis, whereas the other remained free from it. In these instances it must be assumed that tubercle bacilli were present in such a small number that they were insufficient to cause tuberculosis in one of the animals.

To exclude the possibility that race, sex or age influence the persistence of tubercle bacilli within tuberculous lesions, autopsies have been classified as follows:

Race.—White: with lesions from which living tubercle bacilli have been obtained, 31.2 per cent; colored: with lesions from which living tubercle bacilli have been obtained, 38.6 per cent.

TABLE 1.—*Living Tubercle Bacilli in Latent Tuberculous Lesions of Lungs and Tracheobronchial Lymph Nodes*

Number of Autopsy	White or Colored	Male or Female	Age, Years	Cause of Death	Lesions of Lungs	Latent Tuberculous Lesion Inoculated	Result of Inoculation Into 1 or 2 Guinea-Pigs	
2	C	M	58	Endocarditis	Fibrous scars of apical pleura; calcified nodules of lungs and lymph nodes	B, calcified nodule of lymph node	0	
3	W	F	25	Ruptured aneurysm	Calcified nodules of lungs and lymph nodes	A, calcified nodule of lung	0	
4	W	F	50	Carcinoma of cervix	Fibrous scar of left apex; calcified nodules of lungs and lymph nodes	A, calcified nodule of lymph node	0	0
12	W	F	63	Arteriosclerosis; cerebral thrombosis	Calcified nodules of lungs and lymph nodes	A, calcified nodule of lung	0	0
						B, calcified nodule of lymph node	0	0
13	C	M	47	Chronic nephritis	Caseous nodules of lymph nodes	A, caseous nodules of lymph nodes	0	0
16	W	M	70	Chronic nephritis	Fibrous scar of right apex; calcified nodules of lung	A, fibrous scar of apex	0	0
18	C	F	53	Perforated duodenal ulcer	Calcified nodules of lymph node	A, calcified nodule of lymph node	0	
21	W	M	62	Cerebral hemorrhage	Calcified nodules of lungs and lymph nodes	A, calcified nodule of lung	0	0
						B, calcified nodule of lymph node	0	0
23	W	F	16	Purpura hemorrhagica	Caseous encapsulated nodule of lung; caseous nodule of lymph node	A, caseous encapsulated nodule of lung	0	0
						B, caseous nodule of lymph node	0	0
27	C	F	31	Cerebral arteriosclerosis	Calcified nodules of lungs and lymph nodes	A, calcified nodule of lung	0	0
						B, calcified nodule of lymph node	0	0
29	W	M	50	Thrombosis of superior longitudinal sinus	Fibrous scar of apical pleura; caseous nodule of lymph node	A, fibrous scar of apical pleura	0	0
						B, caseous nodule of lymph node	0	0
31	C	M	9	Intestinal obstruction	Caseous encapsulated nodule of lung; caseous calcified nodule of lymph node	A, caseous encapsulated nodule of lung	0	0
						B, caseous calcified nodule of lymph node	0	
34	W	F	70	Carcinoma of face	Fibrous scar of pleura; calcified nodules of lung and lymph node	A, calcified nodule of lymph node	0	0
						B, calcified nodule of lymph node	0	
						C, calcified nodule of lung	0	0
35	W	M	79	Ruptured left ventricle	Fibrous scars of apical pleura; calcified nodules of lungs and lymph nodes	A, calcified nodule of lung	0	0
36	C	F	65	Cerebral hemorrhage	Calcified nodules of lungs and lymph nodes	A, calcified nodule of lymph node	0	0
43	W	M	65	Coronary thrombosis	Calcified nodules of lymph nodes	A, calcified nodule of lymph node	0	0
45	W	M	51	Cerebral hemorrhage	Latent fibrous caseous tuberculosis of right apex; calcified nodules of lymph nodes	A, calcified nodule of lymph node	0	0
						B, fibrous caseous tuberculosis of apex	+	+
						C, calcified nodule of lung	0	0
46	W	M	62	Cerebral syphilis	Fibrous scars of apexes; calcified nodule of lungs	A, calcified nodule of lungs	0	0
50	W	F	80	Arteriosclerosis	Calcified nodules of lungs and lymph nodes	A, calcified nodule of lymph node	0	0
						B, calcified nodule of lung	0	0
53	W	M	55	Arteriosclerosis	Fibrous scar of apical pleura; calcified nodule of lymph node	A, calcified nodule of lymph node	0	0
57	W	M	43	Cerebral hemorrhage	Caseous encapsulated nodule of lung; calcified nodule of lymph node	A, caseous encapsulated nodule of lung	0	0
58	W	M	3	Pott's disease	Caseous calcified nodule and calcified nodules of lymph nodes	A, caseous calcified nodule of lymph node	0	
61	W	F	30	Mitral and aortic endocarditis	Caseous encapsulated nodule of lung; caseous nodule of lymph node	A, caseous encapsulated nodule of lung	0	0

66	W	M	48	Atrophic cirrhosis of liver	Fibrous scar of right apex; caseous encapsulated and calcified nodules of lungs; caseous nodules of lymph nodes	B, caseous nodule of lymph nodes....	0	0
68	C	F	68	Carcinoma of cervix.....	Fibrous calcified scar of left apex; calcified nodules of lungs and lymph nodes	A, calcified nodule of lung.....	+	0
						C, fibrous calcified scar of apex.....	0	0
70	W	M	81	Bronchopneumonia	Fibrous scar of apical pleura; calcified nodules of lung and lymph nodes	A, calcified nodule of lymph node.....	0	
						B, fibrous scar of apical pleura.....	0	0
						C, calcified nodule of lung.....	0	0
72	W	M	49	Cirrhosis of liver.....	Fibrous scar of apical pleura; calcified nodule of lung	A, calcified nodule of lung.....	0	0
73	W	M	43	Cerebral hemorrhage	Caseous encapsulated nodule and calcified nodule of lung; caseous nodule and calcified nodules of lymph nodes	A, caseous nodule of lymph node.....	0	
						B, caseous encapsulated nodule of lung	0	0
						C, calcified nodule of lung.....	0	0
						D, calcified nodule of lymph node.....	0	0
74	W	F	80	Arteriosclerosis	Fibrous calcified scar of left apex; fibrous scar of right apex; calcified nodules of lung and lymph nodes	A, fibrous scar of right apex.....	0	0
						B, fibrous calcified scar of left apex..	+	+
						D, calcified nodule of lung.....	0	
						E, calcified nodule of lymph node.....	0	0
79	C	M	53	Chronic nephritis	Fibrous scar of left apex; caseous nodule and calcified nodule of lung; caseous encapsulated nodule and calcified nodules of lymph nodes	A, calcified nodule of lymph node.....	0	0
						B, fibrous scar of apex.....	0	0
						D, calcified nodule of lung.....	0	0
83	W	F	76	Cerebral hemorrhage	Fibrous scar of apical pleura; calcified nodules of lung and lymph nodes	A, calcified nodule of lung.....	0	0
84	W	M	62	Bronchopneumonia	Fibrous scar of apex; calcified nodule of lymph node	A, fibrous scar of apex.....	0	0
86	W	F	60	Chronic nephritis	Fibrous scars of apexes; calcified nodule of lymph node	A, fibrous scar of apex.....	+	+
						B, calcified nodule of lymph node.....	0	0
87	C	F	64	Chronic nephritis	Fibrous scar of apical pleura; calcified nodule of lung; caseous nodule of lymph node	A, calcified nodule of lung.....	0	0
88	C	M	50	Intestinal obstruction ...	Caseous calcified nodule of lung; calcified nodule of lymph node	A, calcified nodule of lymph node.....	0	0
						B, caseous calcified nodule of lung....	0	
89	W	M	67	Endocarditis	Fibrous scar of apex; caseous calcified nodule of lung; calcified nodule of lymph node	A, calcified nodule of lung.....	0	0
						B, fibrous scar of apex.....	0	0
95	C	F	73	Adenocarcinoma of ovary	Fibrous calcified scar of left apex; fibrous scar of right apical pleura; calcified nodules of lung and lymph nodes	B, calcified nodule of lymph node.....	0	0
						C, fibrous calcified scar of apex.....	0	0
						D, calcified nodule of lung.....	0	0
98	W	M	48	Banti's disease	Calcified nodule of lung.....	A, calcified nodule of lung.....	0	
102	W	M	63	Perforated gastric ulcer..	Fibrous scar of apex; calcified nodules of lungs and lymph nodes	A, calcified nodule of lung.....	0	
						B, calcified nodule of lung.....	0	0
103	C	F	30	General paralysis	Latent fibrous caseous tuberculosis of right apex; calcified nodule of lungs and lymph nodes	B, calcified nodule of lung.....	+	0
						C, fibrous caseous tuberculosis of apex	+	
106	W	F	74	Cardiorenal disease	Fibrous scar of apical pleura; caseous encapsulated nodule and calcified nodule of lung; calcified nodule of lymph nodes	A, calcified nodule of lymph node.....	0	
107	W	F	59	Cerebral softening	Fibrous scar of apex; calcified nodule and caseous calcified nodule of lung; caseous encapsulated nodule of lymph node	A, calcified nodule of lung.....	0	0
						B, caseous calcified nodule of lung....	0	0
						C, fibrous scar of apex.....	0	0
						D, caseous encapsulated nodule of lymph node	0	0

TABLE 1.—*Living Tubercle Bacilli in Latent Tuberculous Lesions of Lungs and Tracheobronchial Lymph Nodes—Continued*

Number of Autopsy	White or Colored	Male or Female	Age, Years	Cause of Death	Lesions of Lungs	Latent Tuberculous Lesion Inoculated	Result of Inoculation Into 1 or 2 Guinea-Pigs	
110	W	M	39	Gunshot wound of femoral vein	Caseous encapsulated nodules of lungs and lymph nodes	A, caseous encapsulated nodule of lung	0	0
111	W	M	45	Bronchopneumonia	Latent fibrous caseous tuberculosis of right apex; caseous encapsulated nodule and calcified nodule of lymph nodes	A, calcified nodule of lymph node.....	+	0
						B, fibrous caseous tuberculosis of apex	+	0
112	W	M	73	Generalized arteriosclerosis	Fibrous scars of apexes; calcified nodules of lungs and lymph nodes	A, fibrous scar of apex.....	0	
						C, calcified nodule of lymph node.....	0	0
113	W	M	51	General arteriosclerosis..	Fibrous scars of apexes.....	A, fibrous scar of apex.....	0	
117	W	M	66	General arteriosclerosis..	Latent fibrous caseous tuberculosis of right apex; calcified nodules of lymph node	A, fibrous caseous tuberculosis of apex	+	+
						C, calcified nodule of lymph node.....	0	0
118	W	F	64	Senile dementia	Calcified nodule of pleura; calcified nodule of lymph node	A, calcified nodule of lymph node.....	+	
						B, calcified nodule of lymph node.....	+	+
128	C	F	25	Pleurisy (streptococcic)..	Fibrous scars of apexes; calcified nodule of lung; caseous nodule of lymph node	A, caseous nodule of lymph node.....	0	0
						B, calcified nodule of lung.....	0	0
130	W	M	50	Lobar pneumonia	Fibrous scar of left apex; calcified nodule of lung and lymph nodes; calcified nodules of mesentery	C, calcified nodule of lymph node.....	0	0
						D, calcified nodule of lung.....	0	0
						E, fibrous scar of apex.....	0	0
131	C	M	46	Chronic myocarditis	Caseous encapsulated nodule of lung; calcified nodule of lymph node	A, calcified nodule of lymph node.....	0	0
						B, caseous encapsulated nodule of lung	0	0
132	W	F	56	Malignant tumor of liver	Fibrous scar of left apex; caseous calcified nodule of lung; caseous encapsulated nodule of lymph node	A, fibrous scar of apex.....	0	0
						B, caseous calcified nodule of lung.....	0	0
						C, caseous encapsulated nodule of lymph node	0	0
136	W	M	72	Cerebral thrombosis	Fibrous scars of apexes; calcified nodule of lymph node	A, fibrous scar of right apex.....	0	0
						B, calcified nodule of lymph node.....	0	0
						C, fibrous scar of left apex.....	0	0
137	W	F	66	Acute endocarditis	Fibrous scar of apical pleura; caseous calcified nodules of lungs and lymph nodes	A, caseous calcified nodule of lymph node	0	0
						B, caseous calcified nodule of lung....	0	0
						C, caseous calcified nodule of lung....	0	0
138	W	F	67	Carcinoma of sigmoid ...	Fibrous scars of apical pleura; caseous nodules of lymph node	A, caseous nodule of lymph node.....	0	0
140	W	M	76	Tumor of lung.....	Latent fibrous caseous calcified tuberculosis of right apex; calcified nodules of lungs and lymph nodes	A, fibrous caseous calcified tuberculosis of apex	0	0
						B, calcified nodule of lymph node.....	0	0
141	W	M	11	Endocarditis	Calcified nodules of lungs and lymph nodes.....	A, calcified nodule of lymph node.....	0	0
142	W	F	28	Burn (roentgen ray).....	Calcified nodules of lungs and lymph nodes.....	A, calcified nodule of lung.....	0	0
						B, calcified nodule of lymph node.....	0	0
143	W	F	101	Arteriosclerosis	Fibrous scar of apical pleura; caseous encapsulated nodule and calcified nodule of lung; caseous nodule and calcified nodule of lymph node	A, caseous encapsulated nodule of lung	0	0
						B, calcified nodule of lung.....	0	
148	C	M	30	Cerebral hemorrhage	Fibrous scar of apex.....	A, fibrous scar of apex.....	0	0

150	W	M	74	Arteriosclerosis	Fibrous scar of apical pleura; calcified nodules of lungs and lymph nodes	A, calcified nodule of lungs.....	0	0
						B, calcified nodule of lymph node.....	0	0
152	C	F	80	Arteriosclerosis	Calcified nodule of lung; caseous encapsulated nodule of lymph node	A, calcified nodule of lung.....	0	0
154	C	M	26	Aneurysm (ruptured) of splenic artery	Fibrous scar of left apex; calcified nodule of lymph node	A, fibrous scar of apex.....	0	
						B, calcified nodule of lymph node.....	0	
156	W	M	37	Fracture of skull.....	Latent fibrous caseous tuberculosis of left apex; calcified nodule of lymph node	A, fibrous caseous tuberculosis of apex	+	+
						B, calcified nodule of lymph node.....	0	0
157	W	F	44	Acute peritonitis	Calcified nodules of lung and lymph nodes.....	A, calcified nodule of lung.....	0	
						B, calcified nodule of lymph node.....	0	
158	W	F	74	Arteriosclerosis	Fibrous scars of apical pleura; caseous encapsulated nodules of lungs and lymph nodes	A, caseous encapsulated nodule of lymph node	0	
						B, caseous encapsulated nodule of lung	0	0
159	W	F	51	Thrombosis of superior longitudinal sinus	Calcified nodule of lymph node.....	A, calcified nodule of lymph node.....	0	
160	W	M	45	Gunshot wound of abdomen	Calcified nodules of lung and lymph nodes; caseous encapsulated nodule of lymph node	B, calcified nodule of lung.....	0	
						C, caseous encapsulated nodule of lymph node	0	
170	W	M	50	Ulcer of duodenum.....	Fibrous scars of apical pleura; calcified nodules of lung and lymph node	B, fibrous scar of apical pleura.....	0	0
171	W	M	64	Generalized arteriosclerosis	Fibrous scars of apexes; caseous encapsulated nodules of lungs and lymph nodes; calcified nodule of lymph node	B, caseous encapsulated nodule of lymph node	0	0
						C, caseous encapsulated nodule of lung	0	0
176	W	M	60	Carcinoma of larynx.....	Fibrous scar of right apex; fibrous calcified scar of left apex; calcified nodule of lungs and lymph nodes; caseous calcified nodule of lymph nodes	A, fibrous scar of right apex.....	+	0
						B, fibrous scar of left apex.....	+	0
						C, calcified nodule of lung.....	0	0
						D, caseous calcified nodule of lymph node	0	0
177	C	M	71	Carcinoma of prostate...	Fibrous scar of right apex; calcified nodules of lungs and lymph nodes	A, fibrous scar of apex.....	0	0
						B, calcified nodule of lung.....	+	0
						C, calcified nodule of lymph node.....	+	+
						D, calcified nodule of lymph node.....	0	0
						E, calcified nodule of lung.....	+	0
179	W	M	55	Diabetes	Calcified nodule of lung.....	A, calcified nodule of lung.....	+	0
180	C	F	55	Chronic nephritis	Fibrous scar of left apex; fibrous scar of right apical pleura; calcified nodule of lymph node	A, fibrous scar of apex.....	0	0
						B, calcified nodule of lymph node.....	0	0
188	W	M	23	Fracture of spine.....	Calcified nodules of lung and lymph nodes.....	A, calcified nodule of lung.....	0	0
189	W	M	61	Chronic nephritis	Fibrous scar of apex; calcified nodule and caseous nodule of lymph nodes	A, fibrous scar of apex.....	+	0
						B, calcified nodule of lymph node.....	+	+
193	W	M	28	Chronic nephritis	Fibrous scar of right apex; calcified nodules of lung and lymph nodes	A, fibrous scar of apex.....	+	+
197	C	F	76	Carcinoma of uterus.....	Fibrous scar of right apex.....	A, fibrous scar of apex.....	0	0
198	W	F	70	Cardiorenal disease	Fibrous scar of left apex; calcified nodule of lymph node	A, fibrous scar of apex.....	0	0
						B, calcified nodule of lymph node.....	0	0
201	W	F	58	Carcinoma of breast.....	Latent fibrous caseous tuberculosis of left apex...	A, fibrous caseous tuberculosis of apex	+	0
204	C	M	50	General paralysis	Fibrous scars of apexes.....	A, fibrous scar of apex.....	+	+
210	W	M	69	Cirrhosis of liver.....	Fibrous scars of apexes; calcified nodule of lymph node	A, fibrous scar of right apex.....	+	0
						B, calcified nodule of lymph node.....	+	+
						C, fibrous scar of left apex.....	0	0

TABLE 1.—*Living Tubercle Bacilli in Latent Tuberculous Lesions of Lungs and Tracheobronchial Lymph Nodes—Continued*

Number of Autopsy	White or Colored	Male or Female	Age, Years	Cause of Death	Lesions of Lungs	Latent Tuberculous Lesion Inoculated	Result of Inoculation Into 1 or 2 Guinea-Pigs	
212	C	F	80	Generalized arteriosclerosis	Fibrous scar of apex; calcified nodule of lymph node	A, calcified nodule of lymph node.....	0	
217	W	M	71	Adenocarcinoma of prostate	Fibrous scars of apexes; calcified nodule of lymph node	A, fibrous scar of apex.....	0	0
						B, calcified nodule of lymph node.....	+	+
218	W	F	80	Arteriosclerosis	Fibrous scar of apical pleura; calcified nodule of lymph node	A, fibrous scar of apical pleura.....	0	0
219	W	M	71	Adenocarcinoma of prostate	Latent fibrous caseous tuberculosis of right apex; fibrous calcified scar of left apex; calcified nodule of lung; caseous nodule of lymph node	A, fibrous caseous tuberculosis of apex	+	+
						B, caseous nodule of lymph node.....	+	0
220	W	F	67	Coronary thrombosis ...	Latent fibrous caseous calcified tuberculosis of left apex; fibrous scar of right apical pleura; calcified nodule of lung	A, fibrous caseous calcified tuberculosis of apex	+	+
222	W	M	60	Adenocarcinoma of gallbladder	Latent fibrous caseous tuberculosis of left apex; fibrous scar of right apex; caseous encapsulated nodule and caseous calcified nodules of lung; calcified nodule of lymph node	A, caseous encapsulated nodule of lung	+	0
						B, calcified nodule of lymph node.....	+	+
						C, fibrous caseous tuberculosis of apex	+	+
223	W	F	65	Carcinoma of breast.....	Fibrous scars of apexes; caseous calcified nodule and caseous nodule of lung; calcified nodule of lymph node	A, fibrous scar of right apex.....	+	+
						B, fibrous scar of left apex.....	0	0
226	W	F	44	Carcinoma of breast.....	Calcified nodules of lung and lymph nodes.....	A, calcified nodule of lung.....	0	
						B, calcified nodule of lymph node.....	0	0
227	W	M	59	Chronic nephritis	Calcified nodules of lungs and lymph nodes.....	A, calcified nodule of lung.....	0	0
						B, calcified nodule of lymph node.....	0	0
236	O	F	67	Chronic gastric ulcer.....	Calcified nodule of lymph node.....	A, calcified nodule of lymph node.....	+	
239	W	M	50	Cerebral hemorrhage	Caseous encapsulated nodule of lung; calcified nodule of lymph node	A, caseous nodule of lymph node.....	+	+
241	♀	M	42	Thrombosis of cerebral vein	Latent fibrous caseous tuberculosis of apexes; calcified nodule of lymph node	A, calcified nodule of lymph node.....	+	+
						B, fibrous caseous tuberculosis of apex	+	+
243	W	M	63	Arteriosclerosis	Caseous calcified nodule and calcified nodule of lung; calcified nodule of lymph node	A, caseous calcified nodule of lung.....	0	0
						B, calcified nodule of lymph node.....	0	0
						C, calcified nodule of lymph node.....	0	0
245	W	M	63	Pyonephrosis	Calcified nodules of lung and lymph nodes.....	A, calcified nodule of lung.....	0	0
						B, calcified nodule of lymph node.....	0	
248	W	M	60	Cerebral hemorrhage	Latent caseous calcified tuberculosis of left apex; caseous encapsulated nodule and caseous calcified nodule of lung; calcified nodule of lymph node	A, caseous encapsulated nodule of lung	+	
						B, caseous calcified tuberculosis of apex	0	0
						D, caseous calcified nodule of lung.....	0	0
						E, calcified nodule of lymph node.....	0	0
249	C	F	42	Aortic aneurysm	Caseous encapsulated nodules of lungs; caseous encapsulated nodules and caseous nodule of lymph nodes	A, caseous encapsulated nodule of lungs	+	0
						B, caseous nodule of lymph node.....	0	
251	W	M	52	Arteriosclerosis	Fibrous scar of left apex; calcified nodules of lungs; caseous calcified nodule of lymph nodes	A, calcified nodules of lymph nodes....	0	0
						B, calcified nodules of lymph nodes....	+	

255	W	F	65	Senile dementia	Fibrous scars of apexes; calcified nodules of lungs and lymph nodes	B, calcified nodule of lung.....	+	
						C, fibrous scar of apex.....	+	+
						E, calcified nodule of lymph node.....	+	+
257	C	F	38	Carcinoma of cervix.....	Calcified nodules of lungs and lymph nodes.....	A, calcified nodule of lymph node.....	+	+
260	W	F	52	Carcinoma of labium....	Fibrous scar of apical pleura; calcified nodule of lung	A, calcified nodule of lung.....	0	0
						B, calcified nodule of lung.....	0	0
261	W	M	70	Arteriosclerosis	Fibrous scar of left apex; calcified nodule of lung	A, calcified nodule of lung.....	0	0
						B, fibrous scar of apex.....	0	0
262	W	M	65	Carcinoma of bladder....	Fibrous scars of apexes; caseous encapsulated nodules and calcified nodule of lungs; caseous nodule of lymph nodes	A, caseous encapsulated nodule of lung	0	0
						B, caseous nodule of lymph node.....	+	+
						C, fibrous scar of right apex.....	+	0
						D, calcified nodule of lung.....	0	0
						E, fibrous scar of left apex.....	0	0
						F, calcified nodule of lung.....	0	0
265	W	M	50	Lobar pneumonia	Fibrous scar of right apex; calcified nodules of lung and lymph nodes	A, calcified nodule of lymph node.....	0	0
						B, fibrous scar of apex.....	0	0
266	W	M	74	Peritonitis	Calcified nodule of lung and lymph node.....	C, calcified nodule of lymph node.....	0	0
267	W	F	74	Cerebral thrombosis	Caseous encapsulated nodule of lung; caseous nodule of lymph node	A, caseous nodule of lymph node.....	+	+
268	W	F	60	Nephritis	Fibrous scar of apical pleura; caseous encapsulated nodule of lung and lymph nodes; caseous nodule of lymph node	A, caseous encapsulated nodule of lung	+	+
270	W	M	65	Senile dementia	Fibrous scars of apexes; caseous encapsulated nodules and calcified nodules of lymph nodes	A, calcified nodule of lymph node.....	+	+
						B, calcified nodule of lymph node.....	+	+
						E, fibrous scar of apex.....	+	+
271	W	M	63	Myocarditis	Fibrous scar of right apex; fibrous scar of left apical pleura; calcified nodule of lymph node	A, fibrous scar of apex.....	0	0
272	W	M	74	Cerebral thrombosis	Latent fibrous caseous calcified tuberculosis of right apex; fibrous scar of left apex; calcified nodule of lung	A, fibrous caseous calcified tuberculosis of apex	+	0
						D, calcified nodule of lung.....	0	
277	C	M	50	Arteriosclerosis	Fibrous scars of apexes; calcified nodules of lymph nodes	A, fibrous scar of apex.....	0	0
278	W	M	64	Epithelioma of tongue..	Latent fibrous caseous tuberculosis of apexes; calcified nodules of lungs; caseous encapsulated nodule of lymph node	A, calcified nodule of lung.....	0	0
						B, fibrous caseous tuberculosis of apex	+	+
281	W	F	68	Hemiplegia	Fibrous scar of left apex; fibrous calcified scar of right apical pleura; calcified nodule of lung; caseous calcified nodule and calcified nodule of lymph node	A, calcified nodule of lung.....	0	0
						B, fibrous scar of apex.....	0	0
288	C	M	49	Diabetes	Latent fibrous caseous tuberculosis of right apex; caseous nodule of lymph node	A, fibrous caseous tuberculosis of apex	0	0
						B, caseous nodule of lymph node.....	+	
289	C	M	64	Senile dementia	Latent fibrous caseous tuberculosis of apex; calcified nodule of lymph node	A, calcified nodule of lymph node.....	0	0
						B, fibrous caseous tuberculosis of apex	+	0
296	C	M	53	Chronic nephritis	Fibrous scars of apexes; calcified nodule of lung; calcified nodule of mesenteric lymph node	A, fibrous scar of apex.....	0	0
297	W	M	60	Lobar pneumonia	Fibrous scar of apical pleura; calcified nodules of lungs and lymph nodes	A, calcified nodule of lung.....	0	0
						B, calcified nodule of lymph node.....	0	0
299	W	M	38	Acute myocarditis	Fibrous scars of apexes; caseous calcified nodule of lungs; calcified nodule of lymph nodes	A, fibrous scar of apex.....	0	0
						B, caseous calcified nodule of lungs....	0	

TABLE 1.—*Living Tubercle Bacilli in Latent Tuberculous Lesions of Lungs and Tracheobronchial Lymph Nodes—Continued*

Number of Autopsy	White or Colored	Male or Female	Age, Years	Cause of Death	Lesions of Lungs	Latent Tuberculous Lesion Inoculated	Result of Inoculation Into 1 or 2 Guinea-Pigs	
300	C	F	73	Adenocarcinoma of intestine	Latent fibrous caseous tuberculosis of right apex; caseous encapsulated nodule of lungs and lymph nodes; calcified nodules of lungs and lymph nodes	A, calcified nodule of lung	0	0
						B, fibrous caseous tuberculosis of apex	0	0
						D, caseous encapsulated nodule of lung	0	
305	W	M	49	Cerebral hemorrhage	Latent fibrous caseous calcified tuberculosis of left apex; fibrous scar of right apical pleura; calcified nodules of lungs and lymph nodes	A, calcified nodule of lung	0	0
						B, calcified nodule of lymph node	0	0
						C, fibrous caseous calcified tuberculosis of apex	+	+
306	C	M	35	Purulent meningitis	Caseous calcified nodule of lymph node	A, caseous calcified nodule of lymph node	0	0
310	C	M	42	Myocarditis	Fibrous scar of right apex; fibrous scar of left apical pleura; calcified nodule of lymph node	A, calcified nodule of lymph node	+	0
318	W	M	68	Chronic myocarditis	Latent fibrous caseous tuberculosis of apexes; calcified nodule of lymph nodes	A, fibrous caseous tuberculosis of apex	0	
						C, calcified nodule of lymph node	0	
320	W	M	67	Arteriosclerosis	Fibrous calcified scar of right apex; calcified nodule of lung	A, fibrous calcified scar of apex	0	
						B, calcified nodule of lung	0	0
322	C	M	17	Peritonitis	Caseous encapsulated nodule of lung; caseous nodule of lymph node	A, caseous nodule of lymph node	0	
						B, caseous nodule of lymph node	+	+
327	C	F	50	Chronic nephritis	Latent fibrous caseous calcified tuberculosis of right apex; fibrous calcified scar of left apex; calcified nodules of lungs and lymph nodes; calcified nodules of mesentery	C, fibrous caseous calcified tuberculosis of right apex	0	0
						D, calcified nodule of lung	0	0
						E, calcified nodule of lymph node	+	+
						F, fibrous calcified scar of left apex	+	
331	W	M	44	Purulent meningitis	Caseous calcified nodule and calcified nodule of lung; caseous nodule and caseous encapsulated nodule of lymph node	A, caseous calcified nodule of lung	+	0
						C, caseous nodule of lymph node	0	0
334	W	M	36	Cerebrospinal meningitis	Caseous calcified nodule of lung; caseous nodule, caseous calcified nodule and calcified nodules of lymph nodes	A, caseous calcified nodule of lung	0	0
						B, caseous nodule of lymph node	0	0
338	W	M	63	Cerebral hemorrhage	Fibrous scars of apexes	A, fibrous scar of right apex	0	0
						C, fibrous scar of left apex	0	0
339	C	M	68	Ruptured aortic aneurysm	Calcified nodules of lungs and lymph nodes; calcified nodule of mesenteric lymph node	A, calcified nodule of lung	0	0
						B, calcified nodule of lymph node	0	
340	C	M	49	Syphilitic aortitis and endocarditis	Fibrous scar of apex; calcified nodule of lung; caseous nodule and calcified nodule of lymph node	B, calcified nodule of lung	+	0
344	W	M	45	Cirrhosis of the liver	Caseous calcified nodule and calcified nodules of lung; calcified nodules of lung and lymph node; caseous and caseous calcified nodule of lymph nodes	A, caseous calcified nodule of lung	0	0
						B, caseous calcified nodule of lymph node	0	0
356	W	M	50	Acute nephritis	Fibrous scars of apical pleura; caseous encapsulated nodule and calcified nodule of lung; caseous nodule and calcified nodule of lymph nodes	A, caseous nodule of lymph node	0	
						C, calcified nodule of lymph node	0	

357	W	M	81	Arteriosclerosis	Latent fibrous caseous tuberculosis of right apex; fibrous scar of left apex; caseous calcified nodule and calcified nodule of lung	A, fibrous caseous tuberculosis of apex	+	+
						C, calcified nodule of lung.....	0	0
						D, caseous calcified nodule of lung....	0	0
373	W	M	62	Adenocarcinoma of pancreas	Latent fibrous caseous tuberculosis of right apex; fibrous caseous calcified tuberculosis of left apex; calcified nodule of mesentery	B, fibrous caseous tuberculosis of right apex	0	
						C, fibrous caseous calcified tuberculosis of apex	0	
374	W	M	67	Traumatic rupture of right ventricle	Latent fibrous caseous tuberculosis of right apex; fibrous calcified scar of left apex	A, fibrous caseous tuberculosis of right apex	0	0
378	W	F	80	Arteriosclerosis	Latent fibrous caseous calcified tuberculosis of left apex; fibrous calcified scar of right apex; caseous calcified nodule of lung; calcified nodule of lymph node; calcified nodule of mesentery	B, fibrous calcified scar of apex.....	0	
						C, calcified nodule of lymph node.....	+	+
382	W	F	31	Acute nephritis	Fibrous calcified scar of left apex; caseous encapsulated nodule of lung; caseous nodule of lymph node	B, caseous nodule of lymph node.....	0	
383	C	F	57	Carcinoma of cervix.....	Fibrous calcified scar of left apex; caseous encapsulated nodules of lungs and lymph nodes	B, fibrous calcified scar of apex.....	0	0
387	W	M	65	Adenocarcinoma of pancreas	Fibrous calcified scar of right apex; fibrous scar of left apex; calcified nodules of pleura; caseous nodule and calcified nodule of lymph nodes	B, calcified nodule of lymph node.....	+	+
						C, caseous nodule of lymph node.....	0	0
388	C	M	60	Unresolved lobar pneumonia	Caseous encapsulated nodule and calcified nodules of lung	A, caseous encapsulated nodule of lung	0	
390	W	M	61	Bronchopneumonia	Latent fibrous caseous tuberculosis of left apex; caseous encapsulated nodule and caseous calcified nodule of lung; caseous calcified nodule of lymph node	A, caseous calcified nodule of lung....	0	
						B, caseous calcified nodule of lymph node	0	0
397	W	F	65	Cardiorenal disease	Fibrous calcified scar of right apex; calcified nodule of lung	A, fibrous calcified scar of apex.....	0	0
398	W	F	70	Arteriosclerosis	Fibrous scars of apexes; calcified nodules of lung and lymph nodes	A, calcified nodule of lung.....	0	0
						C, calcified nodule of lymph node.....	0	
411	W	F	26	Peritonitis	Calcified nodule of lung; caseous calcified nodule of lymph node	A, calcified nodule of lymph node.....	0	0
413	W	M	18	Ruptured duodenal ulcer	Caseous calcified nodules of lungs and lymph nodes	A, caseous calcified nodule of lymph node	0	0
422	C	M	42	Cerebral hemorrhage	Caseous encapsulated nodules of lungs and lymph nodes	A, caseous encapsulated nodule of lung	0	0
						B, caseous encapsulated nodule of lung	0	0
427	C	M	62	Carcinoma of stomach...	Fibrous scar of left apical pleura.....	A, fibrous scar of left apical pleura....	0	0
429	W	F	75	Carcinoma of cervix.....	Latent fibrous caseous calcified tuberculosis of right apex; fibrous caseous tuberculosis of left apex; calcified nodule of lung	C, fibrous caseous calcified tuberculosis of right apex	+	+
						E, fibrous caseous tuberculosis of left apex	+	
430	W	M	83	Arteriosclerosis	Fibrous scars of apexes; calcified nodules of pleura	C, fibrous scar of left apex.....	0	0
431	W	M	28	Hodgkin's disease	Caseous calcified nodule of lung; calcified nodule of lung and lymph node	A, calcified nodule of lung.....	0	0
432	C	M	70	Chronic nephritis	Latent fibrous caseous tuberculosis of left apex; fibrous scar of right apex; calcified nodule of lymph node	B, fibrous caseous tuberculosis of left apex	+	+

TABLE 1.—*Living Tubercle Bacilli in Latent Tuberculous Lesions of Lungs and Tracheobronchial Lymph Nodes—Continued*

Number of Autopsy	White or Colored	Male or Female	Age, Years	Cause of Death	Lesions of Lungs	Latent Tuberculous Lesion Inoculated	Result of Inoculation Into 1 or 2 Guinea-Pigs	
440	W	F	70	Arteriosclerosis	Fibrous scars of apical pleura; caseous calcified nodules of lungs and lymph nodes	A, fibrous scar of right apical pleura..	0	0
						C, caseous calcified nodule of lymph node	0	0
445	W	M	62	Coronary sclerosis	Caseous nodule and calcified nodule of lymph nodes	C, caseous nodule of lymph node.....	+	
450	C	M	40	Chronic nephritis	Caseous encapsulated nodule of lung.....	D, caseous encapsulated nodule of lung	+	+
452	W	M	56	Carcinoma of larynx....	Latent fibrous caseous tuberculosis of right apex; fibrous scar of left apex; calcified nodes of lungs and lymph nodes	A, fibrous caseous tuberculosis of right apex	+	+
						B, calcified nodule of lymph node.....	+	+
						C, calcified nodule of lungs.....	0	0
453	W	F	78	Chronic nephritis	Calcified nodules of lungs and lymph nodes.....	C, calcified nodule of lymph node.....	0	0
456	W	M	50	Acute pericarditis	Calcified nodules of lungs and lymph nodes.....	D, calcified nodule of lymph node.....	0	
466	W	M	67	Bronchopneumonia	Fibrous scars of apexes; calcified nodule of lung; caseous calcified nodule of lymph node	C, fibrous scar of left apex.....	0	0
						E, caseous encapsulated nodule of lymph node	+	+
474	W	M	50	Pulmonary infarct	Fibrous scar of apical pleura; calcified nodule of lung and lymph node	C, calcified nodule of lymph node.....	+	+
483	W	M	50	Bronchopneumonia	Caseous encapsulated nodule and calcified nodule of lung; caseous encapsulated nodule and calcified nodule of lymph nodes	D, calcified nodule of lung.....	0	0
						E, calcified nodule of lymph node.....	0	0
489	W	M	45	Chronic nephritis	Latent fibrous caseous tuberculosis of left apex; fibrous scar of right apex; caseous encapsulated nodule and calcified nodule of lung; calcified nodule of lymph node	A, fibrous caseous tuberculosis of apex	+	
492	W	M	61	Carcinoma of mouth.....	Calcified nodule of lymph node.....	D, calcified nodule of lymph node.....	0	0
494	W	F	86	Arteriosclerosis	Fibrous calcified scars of apexes; calcified nodule of lymph nodes	A, fibrous calcified scar of right apex	0	0
495	W	F	86	Arteriosclerosis	Latent caseous calcified tuberculosis of left apex; calcified nodule of lymph node	C, calcified nodule of lymph node.....	0	0
497	W	M	56	Septicemia	Caseous encapsulated nodule and caseous calcified nodule of lung; caseous calcified nodule of lymph node	C, caseous calcified nodule of lung.....	0	0
608	W	F	67	Chronic nephritis	Fibrous scar of left apex; calcified nodule of lung and lymph node	D, calcified nodule of lung.....	0	0
609	C	M	47	Septicemia	Fibrous scars of apexes; calcified nodules of lungs and lymph nodes; caseous encapsulated nodule of lymph node	A, fibrous scar of right apex.....	0	0
						D, caseous encapsulated nodule of lymph node	0	0
						E, calcified nodule of lymph node.....	0	

Sex.—Male: with lesions from which living tubercle bacilli have been obtained, 35.5 per cent; female: with lesions from which living tubercle bacilli have been obtained, 27.4 per cent.

Age.—The percentage of autopsies with lesions from which living tubercle bacilli have been obtained has been for various age periods as follows: from 10 to 19 years, 25 per cent (of four); from 20 to 29 years, 12.5 per cent (of eight); from 30 to 39 years, 33.3 per cent (of ten); from 40 to 49 years, 43.5 per cent (of twenty-three); from 50 to 59 years, 27.3 per cent (of thirty-three); from 60 to 69 years, 40.8 per cent (of fifty-two); from 70 to 79 years, 26.9 per cent (of twenty-six); from 80 to 89 years, 33.3 per cent (of ten).

Synopses of the data contained in table 1 are presented in tables 2, 3 and 4.

Table 2 shows the incidence of living tubercle bacilli in tuberculous lesions which occurred as circumscribed foci in any part of the lungs or in the adjacent lymph nodes. These lesions had the characters of tuberculosis of childhood and when found in the lungs of adults, perhaps with a few exceptions, had been present during a period of years.

TABLE 2.—*Presence of Living Tubercle Bacilli in Focal Tuberculous Lesions (Childhood Type)*

	Lungs			Lymph Nodes			Percentage of Total (in Lungs and Lymph Nodes) with Living Tubercle Bacilli
	Number Examined	Number with Living Tubercle Bacilli	Percentage with Living Tubercle Bacilli	Number Examined	Number with Living Tubercle Bacilli	Percentage with Living Tubercle Bacilli	
Caseous nodules	..	..	..	14	7	33.3	33.3
Caseous encapsulated nodules	20	5	25	6	1	14.3	23.3
Caseous calcified nodules	14	1	7.1	9	0	0	4.4
Calcified nodules	63	8	12.7	82	21	25.6	20

Fresh caseous lesions of the lungs were not included in the study, and it is probable that the lesions of lymph nodes designated "caseous" were in most instances not early lesions since histologic examination repeatedly demonstrated abundant new formation of fibrous tissue not evident on gross examination. This opinion is supported by the observation that only one third of them contained living tubercle bacilli.

When the figures for lungs and lymph nodes were combined we found living tubercle bacilli in 33.3 per cent of caseous lesions which were in part fibrotic; in 23.3 per cent of caseous encapsulated nodules; in 4.4 per cent of caseous calcified nodules, and in 20 per cent of calcified nodules. We are not able to offer a wholly satisfactory explanation of these differences. It is not improbable that caseous encapsulated nodules in some instances had been in immediate contact with coincident tuberculous lesions which had not yet fully healed. The incidence of living tubercle bacilli in caseous nodules with beginning calcification was much smaller than that in caseous encapsulated nodules,

on the one hand, and in calcified nodules, on the other. The occurrence of living tubercle bacilli in calcified nodules will be considered in more detail later.

Table 3 shows the presence of living tubercle bacilli in apical lesions which were in large part, at least, tuberculous, and were designated adult type because they were situated at the apex of the lungs and were unaccompanied by lesions of adjacent lymph nodes.

In most instances of latent fibrocaseous tuberculosis of the apex—namely, in three fourths of those cases examined—living tubercle bacilli were found. In the remaining one-fourth, with the progress of fibrosis and other evidence of healing, the micro-organism disappeared from the part selected for inoculation, although it may have persisted in some other part of the same lesion.

With the appearance of calcification (fibrocaseous calcified tuberculosis), the incidence of living tubercle bacilli was diminished but remained high, namely, 50 per cent.

Of fibrous scars of the apex including those in which there was some calcification, about one-fourth contained living tubercle bacilli.

TABLE 3.—*Presence of Living Tubercle Bacilli in Apical Lesions (Adult Type)*

	Number Examined	Number with Living Tubercle Bacilli	Percentage with Living Tubercle Bacilli
Fibrocaseous tuberculosis of apex	21	16	76.2
Fibrocaseous calcified tuberculosis of apex	8	4	50
Fibrocalcified tuberculosis of apex	7	2	25.7
Fibrous scar of apex	45	11	24.4
Fibrous scar of apical pleura	6	0	0

It is noteworthy that histologic examination showed that tubercles or other morphologic evidence of tuberculosis were not present in these lesions.

Of six fibrous scars of the apical pleura none contained living tubercle bacilli, but it is not improbable that a larger series would have shown their presence in a few instances.

It has seemed not improbable that tuberculosis produced in guinea-pigs by the injection of suspensions prepared from calcified nodules of the lungs or lymph nodes might be caused by tubercle bacilli derived by dissemination from coexisting tuberculous lesions of the apex. The micro-organism may be present not in the nodule itself but in the tissue surrounding it. Nodules used for inoculation were surrounded by some lung or lymphoid tissue and although excision was made with aseptic precautions, we did not sterilize this tissue because we feared that we might destroy, at the same time, living tubercle bacilli within the calcified nodules.

In table 4 calcified nodules of lungs and lymph nodes were separated into groups in accordance with the character of other lesions found in the lungs with them. Of calcified nodules removed from lungs of

which one or both apexes contained fibrocaseous lesions, 29.2 per cent caused tuberculosis in guinea-pigs. Of calcified nodules from lungs with a fibrous scar in the apex, 30.2 per cent produced tuberculosis when inoculated into animals. On the contrary, in most instances calcified nodules derived from lungs without apical lesions did not contain any living tubercle bacilli, for of calcified nodules derived from lungs in which there were only focal lesions, 8.1 per cent caused tuberculosis in guinea-pigs. It is evident that calcified nodules from lungs with apical lesions produce tuberculosis in guinea-pigs much more frequently than nodules from lungs of which the apexes appear to be normal.

The foregoing figures indicate that demonstrable tubercle bacilli are not derived from these caseous or calcified nodules but are contained in the tissue surrounding it. With this possibility in view we attempted to determine by animal inoculation how frequently pulmonary or lymphoid tissue which has not exhibited lesions of tuberculosis contains tubercle bacilli.

TABLE 4.—*Calcified Nodules of Lungs or Lymph Nodes Classified in Relation to Associated Lesions*

Associated Lesions of Lungs	Number Examined	Number with Living Tubercle Bacilli	Percentage with Living Tubercle Bacilli
Fibrocaseous tuberculosis of apex	24	7	29.2
Fibrous scar of apex	53	14	30.2
Focal lesions only	62	5	8.1

(*a*) Pulmonary tissue selected for examination was obtained from apexes which on gross examination did not contain any lesion suggestive of tuberculosis or any fibrous scars.

(*b*) From the base of lungs, pulmonary tissue free from tuberculous lesions was examined.

(*c*) The lymph nodes without tuberculous lesions which were injected into guinea-pigs were found within the lung substance at the hilum, outside the lung adjacent to one bronchus or below the bifurcation of the trachea.

In the preparation of the suspension for inoculation a considerable quantity of tissue was used. After searing the surface, a block of tissue from 2 to 5 cm. in diameter was excised with aseptic precautions. Several lymph nodes, each about 1 cm. across, were used for the preparation of the injected suspensions. The quantity of tissue used for these tests (table 5) was much greater than that obtained from lesions presumably tuberculous in origin (table 1).

Tissue from apexes of lungs was inoculated into guinea-pigs in twenty-two instances. Subsequent microscopic examination showed that the tissue employed is never entirely normal, for it almost invariably contained accumulations of coal pigment, often immediately below the

TABLE 5.—*Living Tubercle Bacilli in Pulmonary Tissue (Including Pulmonary Lymph Nodes) Not Containing Tuberculous Lesions*

Number of Autopsy	White or Colored	Male or Female	Age, Years	Cause of Death	Lesions of Lungs	Tissue Inoculated	Result of Inoculation Into 1 or 2 Guinea-Pigs	
426	C	F	45	Syphilis; thrombosis of cerebral artery; brain abscess	Caseous encapsulated nodule of lymph node.....	A, apex, right	+	0
						B, lymph node, bifurcation.....	0	0
						C, base, right	+	+
427	C	M	62	Carcinoma of stomach..	Fibrous scar of apical pleura.....	B, base, left	0	0
						C, lymph node	0	0
429	W	F	75	Carcinoma of cervix.....	Latent fibrous caseous calcified tuberculosis of right apex; fibrous caseous tuberculosis of left apex; calcified nodule of lung	A, lymph node, bifurcation.....	0	0
						B, lymph node, right.....	+	+
						D, base, right	+	0
430	W	M	83	General arteriosclerosis..	Fibrous scars of apexes; calcified nodule of pleura	A, base, right	0	
						B, lymph node, bifurcation.....	0	
431	W	M	28	Hodgkin's disease	Caseous calcified nodule of lung; calcified nodules of lungs and lymph nodes	B, lymph node, right.....	0	0
						C, apex, left	0	
						D, base, left	0	
						E, lymph node, bifurcation.....	0	0
432	C	M	70	Arteriosclerotic nephritis.	Latent fibrous caseous tuberculosis of left apex; fibrous scar of right apex; calcified nodules of lymph node	C, base, left	+	+
						D, lymph node, left.....	+	+
434	C	M	25	Lobar pneumonia	Fibrous scar of apical pleura.....	A, apex, left	+	+
						B, base, left	0	
						C, lymph node, left.....	0	0
438	W	F	70	General arteriosclerosis..	Calcified nodule of lung.....	A, apex, right	0	0
						B, base, right	0	0
						C, lymph node, right.....	0	0
						D, apex, left	0	0
440	W	F	70	General arteriosclerosis and senile dementia	Fibrous scars of apical pleura; caseous calcified nodules of lungs and lymph nodes	B, base, right	0	0
						D, lymph node, bifurcation.....	0	0
445	W	M	62	Sclerosis of coronary artery	Caseous nodules and calcified nodules of lymph nodes	A, apex, right	+	+
						B, base, right	0	
						D, lymph node, left.....	+	+
450	C	M	40	Chronic nephritis	Caseous encapsulated nodule of lung.....	A, apex, left	+	+
						B, base, left	+	+
						C, lymph node, left.....	+	+
453	W	F	78	Chronic myocarditis, purulent bronchitis	Calcified nodules of lung and lymph node.....	A, apex, right	0	0
						B, base, right	0	0
454	W	M	47	Chronic myocarditis	.....	A, apex, left	0	0
						B, base, right	0	0
						C, lymph nodes, left.....	0	0
456	W	M	50	Acute pericarditis and pleurisy	Calcified nodule of lungs and lymph node.....	A, apex, right	0	
						B, base, right	0	
						C, lymph node, bifurcation.....	0	0
458	C	F	37	Postpartum hemorrhage.	.....	A, apex, right	0	0
						B, base, right	0	0
						C, lymph node, right.....	0	0

461	C	F	42	Chronic nephritis	Calcified nodule of lymph node.....	A, apex, left	0	0
						B, base, left	+	0
						C, lymph node, left.....	+	0
466	W	M	67	General arteriosclerosis..	Fibrous scars of apexes; calcified nodule of lung; caseous calcified nodule of lymph node	D, base, left	0	
467	C	F	57	Carcinoma of antrum....	Calcified nodule of lymph node.....	A, apex, right	+	+
						B, base, left	+	
474	W	M	59	Chronic nephritis	Fibrous scar of apical pleura; calcified nodules of lung and lymph nodes	A, apex, right	+	+
						B, base, right	+	+
						D, lymph node, left.....	+	+
480	C	M	60	Generalized arteriosclerosis	Fibrous scar of apical left pleura.....	B, base, right	0	
						C, lymph node, right.....	+	
						E, lymph node, bifurcation.....	0	0
483	W	M	50	Cerebrospinal syphilis and aortitis; bronchopneumonia	Caseous encapsulated nodule and calcified nodule of lung; caseous encapsulated nodule and calcified nodule of lymph nodes	A, apex, left	0	
						B, base, left	0	0
						C, lymph node, left.....	0	
489	W	M	45	Chronic nephritis	Latent fibrous caseous tuberculosis of left apex; fibrous scar of right apex; caseous encapsulated nodule and calcified nodule of lungs; calcified nodule of lymph nodes	B, base, right	0	
						C, lymph node, bifurcation.....	0	0
						D, lymph node, right.....	+	+
492	W	M	61	Carcinoma of mouth.....	Calcified nodules of lymph nodes.....	A, apex, right	+	0
						C, base, right	0	0
						G, lymph node, left.....	0	0
494	W	F	86	Senile dementia and arteriosclerosis	Fibrous calcified scars of apexes; calcified nodule of lymph node	B, base, right	+	0
						D, lymph node, right.....	0	0
495	W	F	86	General arteriosclerosis..	Latent caseous calcified tuberculosis of left apex; calcified nodule of lymph node	A, apex, right	0	0
						D, lymph node, left.....	0	0
497	W	M	56	Otitis media with bacteremia	Caseous encapsulated nodule and caseous calcified nodule of lung; caseous calcified nodule of lymph node	A, apex, left	0	0
						D, lymph node, bifurcation.....	0	0
600	C	F	28	Cerebral thrombosis	.....	C, lymph node, right.....	0	0
603	W	F	67	General arteriosclerosis..	Fibrous scar of left apex; calcified nodules of lung and lymph nodes	A, apex, right	+	0
						B, base, right	+	+
						C, lymph node, bifurcation.....	0	0
604	W	M	76	General arteriosclerosis and chronic nephritis	Calcified nodule of lung.....	A, apex, right	0	0
						B, base, right	0	0
						C, lymph node, bifurcation.....	0	0
605	C	M	23	Acute gonorrheal endocarditis	Calcified nodules of mesentery.....	D, apex, left	0	0
						E, base, left	0	0
						F, lymph node, bifurcation.....	0	0
607	C	F	53	Syphilitic aortitis and aortic endocarditis	Fibrous scar of left apical pleura; calcified nodules of lungs	A, apex, right	0	
						B, base, right	0	
						C, lymph node, right.....	0	0
						D, lymph node, right.....	+	
608	C	M	56	General peritonitis	Fibrous scar of apical pleura; calcified nodule of lymph node	C, lymph node, bifurcation.....	0	0
						D, lymph node, right.....	0	
609	C	M	47	Streptococcus cellulitis .. and septicemia	Fibrous scars of apexes; calcified nodules of lungs and lymph nodes	B, base, right	0	
						C, lymph nodes, right.....	0	0

pleura and surrounded by fibrous tissue. Bronchopneumonia and edema were often present. More significant was the presence of fibrous tissue unassociated with anthracosis and replacing the alveoli, situated immediately below the apical pleura and often extending in wedge shaped areas more or less deeply into the lung substance. In some instances, this fibrous tissue, which was usually sclerotic and poor in cells, not only replaced a thin layer of alveoli immediately below the pleura, but also on gross examination appeared to be limited to the pleura. A line of demarcation between thickened apical pleura and apical scars extending into the lung substance did not exist, but when the subpleural layer of fibrous tissue was thin the lesion was designated "fibrous scar of apical pleura."

In two instances tissue was not saved for examination (438, *D* and 458, *A*); in these instances the result of inoculation was negative. In the apexes examined tuberculous lesions were not found.

On microscopic examination, tissue from the bases of lungs, which on gross examination appeared to be normal, was found to be the site of fibrosis less frequently than that from the apexes. Tissue adjacent to

TABLE 6.—*Living Tubercle Bacilli in Tissues Without Tuberculosis (from Adults)*

	Number Examined	Number with Living Tubercle Bacilli	Percentage with Living Tubercle Bacilli
Apex of lung	22	8	36.4
Base of lung	29	9	31
Bronchial lymph nodes	36	9	25

that tested by animal inoculation was examined in all but five instances (426 *C*, 430 *A*, 434 *B*, 461 *B* and 494 *B*). In the remaining lungs a variety of lesions was found, namely, deposit of coal dust with scant fibrosis, bronchopneumonia, congestion and edema. In five instances there were small patches of fibrosis below the pleura or more deeply seated, but lesions of tuberculosis were not found.

Histologic examination of tracheobronchial lymph nodes used for inoculation disclosed one instance in which small caseous encapsulated tubercles were present, and this was omitted from the series. In one instance (456 *C*) histologic examination was not made. In the remaining lymph nodes, advanced anthracosis with some fibrosis was almost invariably present. In five instances there was hyaline degeneration, usually in the form of tortuous columns along the course of capillaries, and hyaline nodules occurred, but their relation to a preexisting tuberculous process was not evident. One instance of Hodgkin's disease was recorded (autopsy 431), but tubercle bacilli were not recovered from two of the lymph nodes used for inoculation.

Table 6 shows the frequency with which living tubercle bacilli were found in the apex of the lung, the base of the lung or the tracheobronchial lymph nodes which did not contain tuberculous lesions. It

is noteworthy that the tissue was obtained from persons who died from causes other than tuberculosis, but the lungs used for the study were otherwise unselected. The presence of latent tuberculous lesions in other parts of the lung was not excluded (table 7).

Living tubercle bacilli were found in slightly more than one third of the apexes examined and only slightly less frequently at the base. By animal inoculation and subsequent culture, tubercle bacilli were obtained from one fourth of the tracheobronchial lymph nodes without tuberculosis.

The foregoing observations may be considered from another point of view. They may be used to determine how frequently living tubercle bacilli may be recovered from the lungs, including the adjacent tracheo-

TABLE 7.—*Autopsies in Which Tissue Without Tuberculous Lesions Was Injected Into Guinea-Pigs*

	Tubercle Bacilli Present	No Tubercle Bacilli
Fibrocaseous tuberculosis of apex	429 432 489	495
Fibrous scar of apex	494 608	430 466 609
Caseous encapsulated or calcified nodules	426 445 450 461 467 474 492 607	431 438 440 453 456 488 497 604 608
Inconspicuous if any lesion (including fibrous scars of apical pleura)	434 480	427 454 458 600 605

bronchial lymph nodes, of persons who die from causes other than tuberculosis. It is evident that the result applicable to the autopsy services of two large hospitals may require some modification when applied to other groups of patients. In view of the widespread distribution of latent tuberculosis, it was not possible to exclude lungs which contained tuberculous lesions but which were obtained from persons in whom tuberculosis was not recognized during life. The ages of the persons examined varied from 20 to 70 years, but the incidence of living tubercle bacilli among the older people was not unusually high. In table 7 the lungs examined are classified in accordance with the character of latent tuberculous lesions, namely, fibrocaseous tuberculosis of apexes, fibrous scars of apexes and caseous encapsulated or calcified nodules of lungs and lymph nodes, but it is noteworthy that the tissue examined did not

include these lesions. The table gives in one column the numbers of autopsies in which the apex, base or adjacent lymph nodes contained living tubercle bacilli demonstrable by animal inoculation, and in another column the numbers of autopsies of which the tissues failed to produce tuberculosis when injected into guinea-pigs.

Table 7 shows that when inoculations were made from the apex, base and lymph nodes in which tuberculous lesions were not present, living tubercle bacilli were found in one or other of these situations in fifteen of thirty-three persons. The incidence of living tubercle bacilli was highest when there had been latent fibrocaseous tuberculosis of the apex, and least when associated lesions were scant or absent. Nevertheless, even when the only lesions of tuberculosis were healed focal nodules, excised pieces of lung or lymphatic tissue without evidence of past or present tuberculosis contained living tubercle bacilli in half of the autopsies examined.

Throughout the study we have kept in mind the possibility that tubercle bacilli may be transferred by mechanical processes, incident to the performance of autopsies, from lungs with advanced tuberculosis to others in which none is apparent. It is evident that conclusions drawn from these observations are contingent on the exclusion of this technical error, and laborious precautions have been taken to avoid it.

We found that calcified tuberculous lesions of lungs and bronchial lymph nodes when inoculated into guinea-pigs cause tuberculosis in a considerable number of instances (table 2). The calcified nodules from which living tubercle bacilli were obtained were in most instances from lungs with tuberculous apical lesions, but tubercle bacilli were recovered from a small number of calcified nodules even though tuberculous lesions of the apex were not present. Since in nearly half of the lungs which we examined without selection living tubercle bacilli have been present in parts of the lung which did not contain tuberculous lesions, it is evident that tubercle bacilli found by inoculation of calcified nodules may be obtained from the surrounding normal tissue, and not from the focus of calcification. The evidence assembled by us demonstrates that tubercle bacilli, with few if any exceptions, had disappeared from tuberculous lesions when calcification made its appearance.

Furthermore, the study showed that lesions of the apex in adults contained living tubercle bacilli in a large part of all instances, namely, in three fourths of fibrocaseous lesions and in one third of instances in which healing resulted in the formation of fibrous scars. Since focal lesions acquired in childhood are in most instances firmly calcified before adult age is attained, it may be assumed that the apical lesion of adults appears at a time when tubercle bacilli have disappeared from the focal lesion. The anatomic characteristics of tuberculous lesions and the search for tubercle bacilli within them do not support

the opinion that the disease in adults is derived from infection acquired in childhood and indicate that apical tuberculosis of adults is an exogenous infection.

The foregoing considerations do not exclude the possibility that massive infection may cause apical tuberculosis before the lesions of childhood have healed. Experiments on animals indicate that resistance to new infection diminishes after complete recovery from a first infection with tuberculosis, but in the presence of progressive disease, immunity against tuberculosis is only relative and may be overcome. Unfortunately, means are not known by which the immunity of children or of adults may be measured.

The adult type of tuberculosis may occur in children who have already survived a first infection and who retain in token of it calcified nodules in the lungs and lymph nodes, so that during the second decade of life, with increasing frequency as age progresses, pulmonary tuberculosis assumes the adult type. An apical lesion acquired during adolescence may manifest itself in early adult life. It has had its origin in the later period of childhood but, preceded by a focal lesion of juvenile type, has appeared as an exogenous infection.

CONCLUSIONS

Latent fibrocaseous tuberculous lesions of the pulmonary apex in most instances contain living tubercle bacilli.

Many fibrous scars of the apexes (approximately one-fourth) contain living tubercle bacilli even though they do not exhibit gross or microscopic evidence of tuberculosis.

Caseous encapsulated or calcified tuberculous nodules of lungs or lymph nodes seldom (in 9 per cent of the cases) produce tuberculosis when inoculated into guinea-pigs unless they are derived from lungs in which there is an apical lesion.

Lung tissue from the apex or base of the lungs in which tuberculous lesions are not present often causes tuberculosis when inoculated into guinea-pigs, and, likewise, tracheobronchial lymph nodes which do not contain tuberculous lesions often contain living tubercle bacilli.

When pieces of tissue without tuberculous lesion from apex, base and tracheobronchial lymph nodes are examined by animal inoculation, living tubercle bacilli are found in one or another part in slightly less than one half of all persons.

Living tubercle bacilli demonstrated by injecting suspensions prepared from caseous encapsulated or calcified lesions of lungs or tracheobronchial lymph nodes are derived, with few if any exceptions, from the adherent lung or lymphoid tissue and not from the lesion itself.

Apical lesions of adult life make their appearance at a time when lesions caused by tuberculous infection of childhood no longer contain living tubercle bacilli; they occur as the result of exogenous infection.

METASTATIC MELANOMA OF THE JEJUNUM

REPORT OF A CASE *

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While metastatic melanoma of the rectum [1] is not uncommon, metastatic melanoma of the jejunum [2] is rare and only a few cases are reported. The article of Cox and Sloan [3] gives a short survey of the recent literature and a report of a case of a primary melanoma of the jejunum. The following case came under my observation:

REPORT OF CASE

History.—The patient, a white man, aged 50, was brought to the psychopathic division of the hospital, service of Dr. L. J. Karnosh, on account of a mental disturbance. Physical examination revealed a tumor of the liver and enlarged lymph nodes in the left supraclavicular region. He died shortly after admission, before a roentgen-ray examination could be made. The clinical diagnosis was carcinoma of the stomach, with metastasis to liver and lymph nodes.

The past history showed that a small mole was removed from the right chest near the nipple two years previously. The histologic diagnosis at that time was melanoma. A year later one left supraclavicular lymph node and one right axillary lymph node were removed and showed histologically a melanotic tumor.

Autopsy.—The body was well developed and undernourished. A linear scar about 5 cm. in length was seen in the left supraclavicular region, and a similar one in the right axillary region. Around the right nipple was a superficial area of scar tissue (8 by 12 cm.), which showed the remains of old skin grafts. The abdomen was flat. There was a right hydrocele. The left pleura was the seat of an acute fibrinopurulent pleurisy. The right pleural, pericardial and peritoneal cavities appeared normal. The liver extended 6 cm. below the costal margin. Mediastinal lymph nodes were not enlarged. The peritoneal lymph nodes in the region of the mesenteric attachment were enlarged and of a rather firm consistency. On cut section they showed a loss of the normal architecture. The cut surface was mottled gray and brown and of granular appearance. The left inguinal, left supraclavicular and right axillary lymph nodes were enlarged, fused by confluence and similar in appearance to the mesenteric nodes.

Heart: The heart weighed 425 Gm. Except for a moderate hypertrophy and slight sclerosis of the coronary arteries the organ did not show any abnormalities.

Lungs: The right lower lobe showed a lobar pneumonia (early gray hepatization). The left lung and the remainder of right lung were normal.

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* From the Department of Pathology of Cleveland City Hospital and Western Reserve University School of Medicine.

1. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922.

2. Dawson, J. W.: The Melanomata, Their Morphology and Histogenesis, Edinburgh, M. J. **32**:501, 1925.

3. Cox, H. H., and Sloan, R. H.: Melanoma, J. A. M. A. **82**:2021 (June 21) 1924.

Liver: The liver weighed 3,325 Gm. It was markedly enlarged. The right lobe was rounded and appeared globular. The organ cut with decreased resistance. On cut section the right lobe showed a large circumscribed tumor mass, about 12 cm. in diameter. A similar but somewhat smaller tumor (10 cm. in diameter) was found in the left lobe. They were grayish white with a diffuse brown mottling and consisted of a friable material of finely granular appearance. The liver tissue between the tumor masses was light brown. The architecture of the cut surface was obscured. The gallbladder contained a large amount of thin liquid bile. The bile passages were patent.

Kidneys: The combined weight was 225 Gm. The kidneys showed a typical nephrosclerosis of the arteriolar variety. In addition, small, grayish yellow nodules from 2 to 10 mm. in diameter were seen throughout the cortex. They were firm in consistency and well circumscribed. On cut section they showed a granular cut, yellow surface without any sign of melanotic pigment.

Gastro-Intestinal Tract: The esophagus, stomach and duodenum did not present anything unusual. In the proximal portion of the jejunum there was a projecting fungating mass from 5 to 7 cm. in diameter. It was situated opposite the mesenteric attachment and occupied almost the entire intestinal lumen. The tumor was of soft consistency and dark gray, and showed a large amount of black pigment. The surface was slightly ulcerated and partially necrotic. The tumor involved the mucosa, submucosa and muscularis. Two smaller tumors were present in the ileum; these were of a similar color, situated at the mesenteric attachment, and apparently originated in a mesenteric lymph node. They showed marked ulceration and necrosis.

The remainder of the organs did not show anything unusual.

Brain: The dura mater and arachnoid were of normal appearance. The surface of the right frontal lobe showed a yellowish brown tumor of soft consistency. The tumor was 1 cm. in diameter, was attached to the arachnoid and pia mater, and extended into the meditullium. It had a finely granular cut surface, was well circumscribed and was easily removable. Sections of the brain disclosed two other tumor nodules of similar size and appearance, situated in the meditullium just below the right precentral gyrus and the left inferior temporal gyrus.

Microscopic Examination.—The sections were taken from various portions of the metastatic nodules, fixed in a 10 per cent solution of formalin, embedded in paraffin and cut 5 microns thick. The sections were stained with hematoxylin-eosin, Mallory's connective tissue stain, lithium carmine and lithium carmine combined with potassium ferrocyanide (Schmorl[4]). Sections taken from the tumor of the jejunum showed numerous spindle cells with rich cytoplasm, and large, pale, round and polyhedral cells with a finely granular cytoplasm. The cells varied in size, shape and staining quality, and showed numerous mitotic figures. In some fields the cells appeared in alveolar arrangement. The nuclei were large, oval or round, and vesicular. Some of the cells were pigmented, containing a dark brown, amorphous material. There was little or no stroma. Numerous vessels were present, mostly in the form of vascular slits. The cells invaded the submucosa and, to a slight extent, the muscularis. Extensive necrosis was seen on the surface of the tumor. Sections taken from other metastatic nodules presented practically the same picture.

Sections stained with lithium carmine showed the pigment in its original color, a light orange. The iron reaction was negative. Mallory's connective tissue stain

4. Schmorl, G.: Die Pathologisch Histologischen Untersuchungsmethoden, Leipzig, F. C. W. Vogel, 1922.

Fig. 1.—Metastasis of melanoma in jejunum simulating a primary tumor.

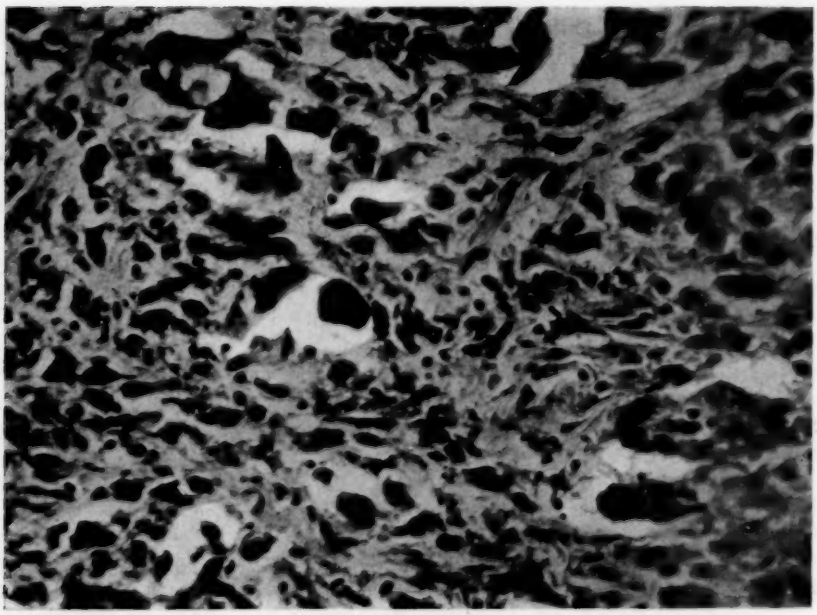

Fig. 2.—Photomicrograph of metastasis of melanoma in jejunum, to show pleomorphism of cells, pigment granules and one mitotic figure. Hematoxylin and eosin stain. Objective 8 mm. Ocular 10 X.

did not reveal any newly formed connective tissue. The kidney sections did not show any melanomas. The nodules described grossly proved on histologic examination to be multiple adenoma.

COMMENT AND SUMMARY

The case here reported deals with a primary melanoma in the region of the right nipple, with metastasis to the supraclavicular, axillary, inguinal and mesenteric lymph nodes, to the liver, jejunum and brain. Signs of a local recurrence were not evident. The fact that the metastatic tumor of the jejunum arose at a point just opposite the mesenteric attachment indicates that the tumor originated in the intestinal wall. The smaller tumors in the ileum arose from the region of the mesenteric attachment, which shows that they originated in the masenteric lymph nodes.

It is interesting that, as in the case of Cox and Sloan, there were not any clinical signs of intestinal obstruction, although the tumor almost completely occluded the lumen.

The absence of a local recurrence of the primary tumor, the hardly noticeable surgical scar on the right chest and the unusually large fungating melanotic tumor of the jejunum arising from the wall opposite the mesenteric attachment suggest that similar large tumors of the jejunum may have been considered primary melanotic tumors. Reports of primary melanotic tumors of the intestine should, therefore, be regarded with suspicion.

GROSS AND MICROSCOPIC ANATOMY OF TWO PERUVIAN MUMMIES *

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The purpose of this study was to determine what possibilities may exist for the identification, by means of the examination of the soft tissues of American mummies, of diseases of the Indians prior to the discovery of America. Peruvian mummies are bodies that have been preserved chiefly, if not wholly, by means of drying; the viscera are said to have been removed sometimes, and sometimes not. MacCurdy [1] states that embalming substances were used to a certain extent, and that analyses by Reutter disclosed the presence of "Balsam of Peru, menthol, salt, tannin, alkaloids, saponins and undetermined resins." Stress was laid on cinnamic acid as a constituent of some of the substances used. Peruvian mummies differ, therefore, from most Egyptian mummies, for in Egypt the bodies were usually given a prolonged soaking in brine (natron), and also resins and other preservatives were used to a large extent. However, the preservation of Egyptian mummies is due partly, and in some cases wholly, to the dry atmosphere of the country. In the southwestern states of this country also, bodies mummified by drying have been found, but I have not been able to secure one for examination.

I am indebted to the trustees of the Field Museum of Natural History, Chicago, for the material used for the present study. It was given to me with the following description: "A Mummy bundle, excavated by Prof. A. L. Kroeber, at excavation 15, Arambaru, Valley of Lima, belonging to the Proto-Lima period, probably between two or three centuries of A.D. 700."

The bundle consisted of about a dozen pieces of cane some 6 feet (183 cm.) in length, tied with grass cord, and contained a gourd, other small articles and some cotton cloth; also a skeleton, the limbs of which were not flexed, and from which several vertebrae and one arm were lacking. When the first skeleton was lifted out, a second skeleton was found beneath it. From this the head, the upper extremities and some of the ribs were missing; otherwise it was complete from the fourth cervical vertebra down. The upper skeleton was probably that of a male; the lower, that of a female. In both cases the bones of the thorax and abdomen were bare, and there were no vestiges of the organs except a few fragments of dried tissue.

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* Read at the Meeting of the American Anthropological Association and the Section on Anthropology of the American Association for the Advancement of Science, December, 1926.

1. MacCurdy: Am. J. Phys. Anthrop. **6**:217, 1923.

The diaphragm, however, was well preserved in the lower (probably female) skeleton, and the pelvis was packed full of carbonized cloth which adhered to the pelvic bones. The spine showed marked new growth of bone at the edges of the vertebrae, producing well defined lips, which were pronounced in the lumbar region. At three points, the third and fourth dorsal, the twelfth dorsal and first lumbar and the first and second lumbar segments, the new formed lips of bone had united, producing ankylosis. This presented, therefore, a notable case of spinal osteo-arthritis (arthritis deformans or spondylitis deformans). This disease, or closely allied conditions, appears to have been widespread among fossil vertebrates—the mammals of the Pleistocene Period, such as the cave-bear—among the ancient Peruvians and among the Egyptians, ancient and modern.[2] The same skeleton had a short ankylosed thirteenth rib on the right side; an articulation for a thirteenth rib was present on the left side, but the rib was missing.

The skull belonging to the upper (probably male) skeleton was empty, except for a few pebbles, some sand and what looked like pieces of dried bark in which characteristic structure could not be determined. Close to the skull lay a quantity of black hair, in which evidence of lice was not found. There was an oval depression about 1 by 2 cm. over the middle of the right parietal bone, close to the sagittal suture; the floor of the depression consisted of rather spongy bone; a roentgenogram showed the skull to be very thin at this point. The depression was probably caused by traumatism, possibly by an attempt at trephining. The left eye was in position, with bits of cloth adhering to it. What appeared to be the cornea could be plainly made out, although the posterior part of the eye was reduced to the consistency of a dry chip of wood. Microscopic study of the eye has not revealed anything of importance. The teeth, which were mostly in position, showed only a little dental caries, and were not as worn as they frequently are in primitive races. The condition of the alveolar processes showed that no teeth had been lost during life. The last two molars were absent from the upper jaw, and a roentgenogram showed that no rudiment of these teeth was present in the jaw.

The one upper arm and the four thighs of the two skeletons were practically bare down to the bones. The material available for study of the soft parts therefore consisted of one forearm and four legs. These parts had been tightly wrapped with cloth, fragments of which, now

2. Moodie: Paleopathology, Urbana, Ill., University of Illinois Press, 1923. MacCurdy: Am. J. Phys. Anthrop. **6**:217, 1923. Hrdlicka: Smithsonian Institution, Reports for 1914. Ruffer: Paleopathology of Egypt, Chicago, University of Chicago Press, 1921. Smith, G. E., and Dawson, W. R.: Egyptian Mummies, London, Allen & Unwin, 1924. Jones, F. W.: Archaeological Survey of Nubia, Reports for 1907-1908, published 1910, vol. 2.

carbonized, adhered to them in many places. It was found that after the limbs were soaked for a few hours in a weak solution of formaldehyde quite a satisfactory dissection could be made. All the finger and toe nails were missing. The principal muscles were readily identified, and their tendons could be traced without difficulty. The tendons running to the bones of the fingers and toes were isolated, so that they appeared nearly as distinct as in a fresh subject, though they were much more fragile. The sciatic nerve was followed from the thigh into its branches for the leg. The posterior tibial artery and nerve and the plantar nerve were traced through a large part of their respective courses.

MICROSCOPIC STUDY

Portions of various tissues were placed for one or two days in 1 per cent formaldehyde solution, and then changed to alcohol, after which they were embedded in collodion or paraffin. In most cases, collodion embedding was the more successful, as the tissues became hard and brittle with paraffin embedding. After more experience with this kind of material, one should not anticipate any difficulty in securing good sections. Various stains were tried, but chiefly hematoxylin and eosin. The nuclei of the cells failed to stain in all of the tissues examined. Dark particles, supposed to be from the soil, were seen in most sections, and sometimes bits of cotton fiber and other vegetable matter and fragments of minute arthropods. Many of the tissues, but most notably certain samples of muscle, showed numerous round or oval yellow to brown masses, from about 8 to as large as 40 microns in diameter. Such masses appeared often to consist of smaller lumps of irregular size. Frequently the outlines were so definite as to suggest that they were cells, and they often contained small dark granules. Various possibilities were entertained to explain their presence, i. e., that the yellow masses might be precipitated products of decomposition; that some of the structures could be phagocytic body cells; that they could be ameboid organisms which invaded the subjects from without; that some of them might be the feces of the arthropods mentioned previously, or that some of the bodies might represent the sporangia of a fungus. In certain sections what appeared to be hyphae were demonstrated, but they were so rarely connected with the yellow masses that the apparent relation may have been accidental. The same bodies will be discussed later in connection with the subject of blood corpuscles.

Numerous bacteria were seen in various sections stained with methylene blue. These were not considered of particular importance; they may have been bacteria of putrefaction that grew into the mummies during the process of drying. However, if the bodies had been given suitable conditions of warmth and moisture at any subsequent period, a bacterial invasion would again have been possible.

Although numerous samples of skin were examined, neither the epidermis nor the glands of the skin could be identified; there were a few doubtful remnants of epidermis between the fingers and toes. Rather unexpectedly, it was found that some elastic fibers in the connective tissue took Weigert's elastic tissue stain well. The adipose tissue, of which there was but little, was easily recognized. The connective tissue of the nerve trunks showed its usual arrangement, but the nerve fibers were represented by empty spaces or by formless débris.

In sections of the posterior tibial and peroneal arteries, the layers of the wall were readily found and the internal elastic membrane could be recognized, but there was not any trace of the endothelium. The

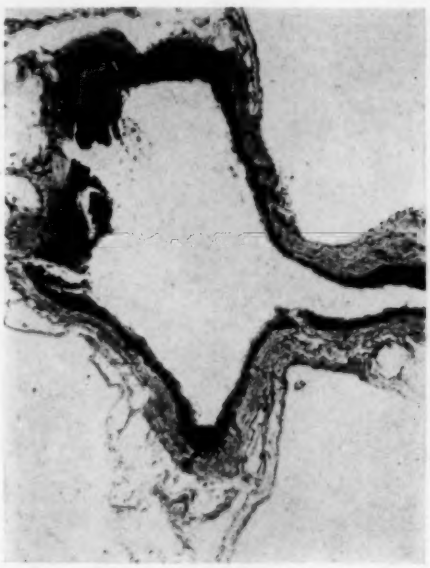

Fig. 1.—Posterior tibial artery of the lower (probably female) subject, stained with nitrate of silver followed with eosin, showing slight thickening of the intima, with calcification, and a calcified thrombus.

elastic membrane did not stain satisfactorily with Weigert's stain. The right posterior tibial artery of the lower (probably female) subject showed in sections a moderate thickening of the intima, and at one point the thickened region was roughened, with a large lateral yellowish mass adhering to it. The artery wall at this point showed granules and masses that blackened with nitrate of silver, while the adherent mass within the artery became intensely black. Without doubt, the conditions were arteriosclerosis, which showed calcification, and a calcified thrombus (fig. 1).

One of the most unexpected results was the presence of cross striations on some of the skeletal muscle fibers, though only on a minority

of them. The striations were visible both in sections and on fibers teased in weak acetic acid and glycerol. As they were also found in a fragment of muscle from a third mummy, it can now be said that striations were demonstrated in the muscles of all three mummies examined (fig. 2).

Still more unexpected was the presence of what appeared to be red blood corpuscles in the tissues of one, and probably of both, of the mummies. In the upper (probably male) subject, circular bodies in considerable masses were found in a section of muscle. The bodies were yellowish brown and showed the characteristic biconcave disk form of red corpuscles, but many of them were larger, measuring

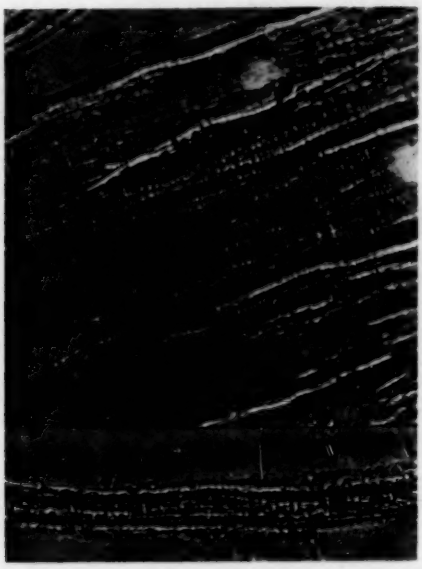

Fig. 2.—Skeletal muscle fibers from the lower (probably female) subject, teased in glycerol, showing cross striations.

8 or even 9 microns occasionally (fig. 3). When it is known what vicissitudes the tissues may have undergone in the way of soaking, drying or compression, and when one remembers the soaking in weak formaldehyde solution given them by me, the increase in size seems not an insuperable objection. I have found about as many red corpuscles with these large diameters in film preparations of normal blood and in faintly staining red corpuscles which occurred within the air vesicles in a case of edema of the lung. The masses of corpuscles in the previously mentioned section from the mummy were free in the tissue; sometimes they stained well with eosin and poorly with methylene blue. The adjacent tissue showed a massive yellow-brown

stain. Numerous round and oval bodies several times as large as the red corpuscles also occurred in the vicinity, and these were crowded with yellow or rarely small black granules. Filaments that stained with methylene blue seen in the same region were regarded as the hyphae of a mold; other filaments appeared to be threads of fibrin. The bodies which appeared to be red corpuscles, were so characteristic that I do not think they could be confused with the spores of a mold, although that possibility should be entertained. The section was interpreted as showing an old hemorrhage, with survival of a few of the red corpuscles but with disintegration of the majority of them. Possibly some of the large pigmented bodies may have been phagocytic cells that engulfed

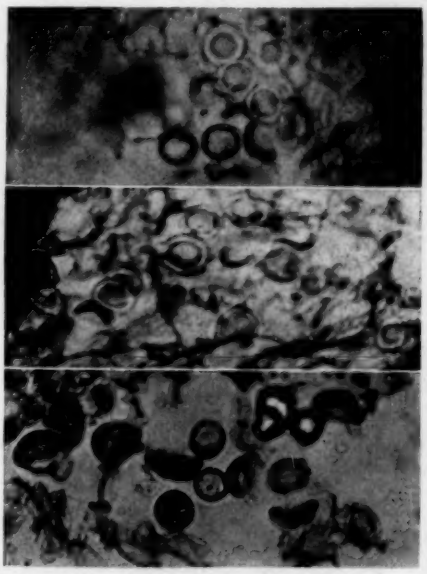

Fig. 3.—What were believed to be red blood corpuscles from a hemorrhage into the muscle of the upper (probably male) subject; sections stained with hematoxylin and eosin. The illustration includes parts of three different fields, so as to bring out as many characteristic forms as possible. The photographs were taken at different times, and there are slight differences in magnification.

granules of blood pigment. The sections gave a well marked iron reaction by the ferrocyanide and hydrochloric acid method, in the form of a diffuse greenish blue stain with a few granular blue masses, not within cells. The reaction was not improved by previous treatment with hydrogen peroxide. It is, of course, possible that the iron was derived from the soil in which the body was interred, but, on the whole, the presence of iron is a rather strong argument to show that an old blood clot was present. Attempts to secure hemin crystals with sodium chloride and acetic acid were not successful. Sections of the

skin of the foot of the upper subject showed a few similar disk-shaped bodies scattered through the deep connective tissue.

Sections of the skin of the foot of the lower (probably female) subject showed similar disk-shaped bodies, which sometimes seemed to lie within small veins. Some of the bodies were large and pale, while others were small (from 4 to 5 microns), with a distinct brown tinge, and often occurred in chains or rows (fig. 4). The possibility that the spores of a mold or other fungus are present in these chains must be considered seriously. Mycelium or other fungus was not observed in the adjacent tissue in this case.

Ruffer [3] in "Studies on the Paleopathology of Egypt" gives an account of his investigations on the histology of Egyptian mummies.

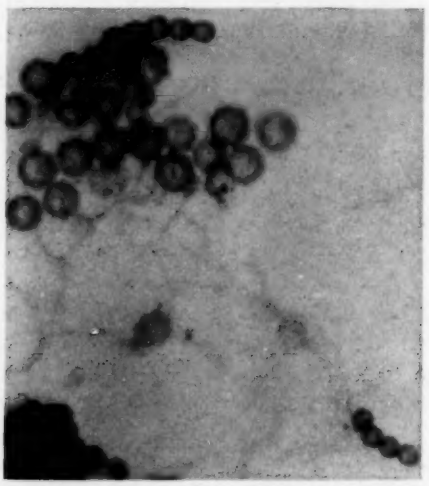

Fig. 4.—What were possibly, if not probably, red blood corpuscles from a section of the skin of the lower (probably female) subject, stained with hematoxylin and eosin. The small forms, in chains, resembling spores or cells of a fungus, are shown.

He easily demonstrated the cross-striations of muscles, and succeeded in staining nuclei in various tissues and in defining the main features of the structure of such organs as the lung, liver and kidney. He states [4] that he was not able to find undoubted red blood corpuscles, although he examined many hundred specimens. Moodie [5] has described and discussed what are possibly fossilized blood corpuscles in the bones of dinosaurs.

3. Ruffer: Studies on the Paleopathology of Egypt, Chicago, University of Chicago Press, 1921.

4. Ruffer (footnote 3, p. 56).

5. Moodie: Paleopathology, Urbana, Ill., University of Illinois Press, 1923, p. 165.

Finally, my colleague, Prof. Carl O. Lathrop, having prepared rabbit serum that gave a strongly positive precipitin test for human serum, tried it with extracts from the dried muscle tissue of both mummies, but his results were negative. Using a rabbit sensitized to human serum, he endeavored to secure a reaction of anaphylaxis with mummy muscle extract, but had only negative results. This is in agreement with Uhlenhuth and Weidanz,[6] who failed to get positive precipitin reactions from twenty-seven Egyptian and Peruvian mummies, and who had only two slight results from sixteen attempts to obtain reactions of anaphylaxis. Meyer,[7] however, has reported success with the precipitin test in two Egyptian mummies stated to be 2,000 and 4,000 years old, respectively.

SUMMARY

In two Peruvian mummies examined, the muscles, tendons, large arteries and nerves were easily identified by dissection.

On microscopic examination, the connective and adipose tissues were recognizable without difficulty. In certain areas, elastic fibers stained well with Weigert's stain for elastic tissue. Epidermis was not found in any of the samples examined. A nuclear stain was not secured in any section.

In sections of one posterior tibial artery, the layers of the wall were recognizable, the intima was thickened and calcified, and a calcified thrombus was attached to the roughened intima.

A portion of the skeletal muscle fibers in these two and in a third mummy showed cross striations.

What were believed to be red blood corpuscles were seen in one of the bodies and possibly in both. The preservation of red corpuscles must be regarded as exceptional and they occurred only in certain favorable areas. Attempts to get precipitin and anaphylactic reactions for human serum were not successful.

One of the subjects exhibited well marked spinal osteo-arthritis.

The results enumerated encourage the belief that in mummies which have the thoracic and abdominal viscera in position, considerable success could be achieved in recognizing pathologic conditions and possibly in determining the cause of death.

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6. Uhlenhuth and Weidanz: Ztschr. f. Morphol. u. Anthrop. **18**:671, 1914.
7. Meyer: München med. Wchnschr. **51**:663, 1904.

LEIOMYOMA OF THE APPENDIX

REPORT OF A CASE

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AND
G. PARCHER, M.D.
P. A. Surgeon and Surgeon, Respectively, U. S. Public Health Service
WASHINGTON, D. C.

Eight cases of primary myoma of the appendix are reported in the literature. Kelly [1] reports two cases, both fibromyomas being situated in the muscular coat and accompanied by chronic appendicitis. Hayem [1] reports one case of myoma with chronic appendicitis. Corner [2] reports a submucous fibromyoma in the distal end of a chronically inflamed appendix. Stickney [3] reports five small submucous myomas in the clubbed end of the appendix. Chronic inflammation and fibrosis of the muscular coat were present. Redway [4] reports two cases, both with chronic inflammatory changes and both in the distal end; in one there was moderate fibrosis of the muscularis and in the other some fibrous growth, but the bulk of the tumor was muscle. Podestá and Pividal [5] describe a fibromyoma originating from the muscularis and projecting externally in an otherwise normal appendix. Dougal's [6] adenomyoma of the appendix was, apparently, as the author states, an implantation from a uterine or ovarian growth of the same character, and is therefore not to be included in the primary myomas of the appendix. The following case was observed by us.

REPORT OF CASE

J. M., aged 40, a white man, complained of abdominal pain and distress for six or seven years. He was admitted to the U. S. Marine Hospital at Portland, Maine, Oct. 27, 1926, with symptoms suggesting chronic appendicitis and gallbladder disease. Laparotomy, November 17, revealed many old adhesions about the gallbladder and pylorus. The gallbladder wall was thin and stones were not palpable. The adhesions were broken up, but the gallbladder was not removed. The appendix was covered with dense adhesions. An appendectomy was performed.

The appendix was thick and bulbous throughout. It was opened lengthwise and fixed in formalin. On receipt at the Hygienic Laboratory, one-half presented

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1. Kelly, H. A., and Hurdon, E.: The Vermiform Appendix and Its Diseases, Philadelphia and London, J. B. Lippincott Company, 1905, p. 739.
2. Corner: M. Press & Circ. **88**:325, 1909.
3. Stickney, S. L.: Bull. Johns Hopkins Hosp. **26**:304, 1915.
4. Redway, Laurence: Leiomyoma of the Appendix, J. A. M. A. **69**:2175 (Dec. 29), 1917.
5. Podestá, A., and Pividal, A. R.: Semana méd. **30**:614, 1923.
6. Dougal, Daniel: J. Obst. & Gynec. Brit. Emp. **30**:224, 1923.

on its inner surface three nodules about 5 mm. high and 5 mm. in diameter. Cross sections of this half, and longitudinal sections of the other, were made and stained with hematoxylin and eosin, and with iron hematoxylin and van Gieson's picrofuchsin.

There was some round-celled infiltration of serosa, muscularis and submucosa, and fibrosis of serosa, submucosa and mucosa. The muscularis mucosa was thickened and irregular, and at one point in the submucosa there was a rounded nodule of muscle tissue with little or no fibrous stroma, and irregularly disposed bundles of muscle fibers. The tunica muscularis was greatly thickened, especially the circular layer. This layer was mostly regular in the disposition of its fibers. On the inner side, a number of loose fiber bundles were present in the submucosa, usually parallel with the circular layer, but occasionally somewhat irregular. The outer longitudinal layer showed marked irregularity of fiber

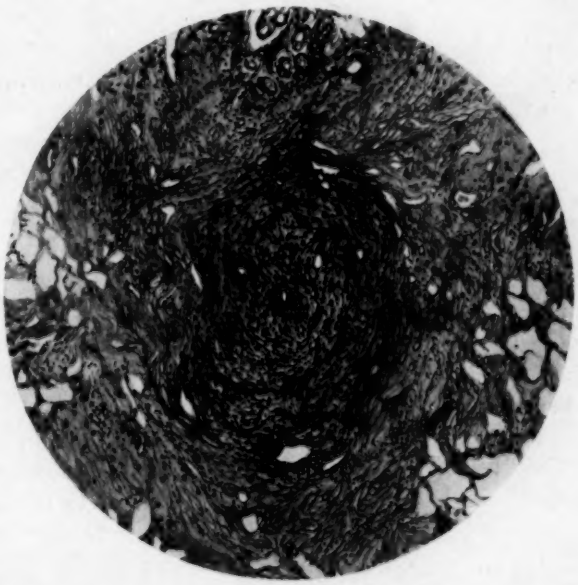


Fig. 1.—Microscopic appearance of leiomyoma in submucous coat of appendix. × 60. Iron hematoxylin and Van Gieson stain.

direction, some fibers running vertical to the surface and some running in a circular direction. At least three much-thickened myomatous areas were noted in a longitudinal section, and one nodule projecting into the serosa. In all of these practically no connective tissue stroma was seen (van Gieson stain).

SUMMARY

A case of leiomyoma of the appendix is reported and the literature reviewed, showing eight previously reported cases. The case under present consideration was pure myoma, rather than fibromyoma, and it occurred in a chronically inflamed appendix. None of the symptoms in this case or in those in the literature is necessarily attributable to the presence of myoma.

Laboratory and Clinical Notes

A SILVER TANNATE TECHNIC FOR PARAFFIN SECTIONS FROM THE CENTRAL NERVOUS SYSTEM*

N. C. Foot, M.D., Cincinnati

The achievements of the Spanish school of neurohistologists under the leadership of Ramón y Cajal, in respect to the demonstration of various elements in the central nervous system, are too well known to students of neurology and neuropathology to require an elaborate introduction. Bailey (Bailey and Hiller,[1] 1924; Bailey and Cushing,[2] 1926) has been popularizing these methods in this country, using them in his neuropathologic investigations which have contributed so much to the knowledge of the tumors of the glioma group.

The technic employed by the Spaniards depends almost entirely on impregnations of tissue with the salts of silver or gold, or both, but there is one drawback—the fact that they are applied either to blocks of tissue, before sectioning, or to frozen sections. There is always a wealth of neurologic material in large pathologic laboratories, but as many of them use the Zenker fixation as a routine measure and cut the tissue in paraffin, much of it is unavailable for metallic impregnations. Thus, the technicians become used to this routine and acquire relatively little proficiency in frozen section technic, while the busy resident pathologists are apt to neglect formalin fixation if it entails extra jars and additional labor. Furthermore, frozen sections are not easily handled without the risk of considerable mutilation, and this is especially true if they must be transferred through a number of baths and washes. If they are mounted on glass slides by the celloidin method of Mallory and Wright[3] (1924), this mutilation can be avoided, but a new element of error is introduced by the film of celloidin used to fix the sections to the slides; it may vary in thickness, become unevenly distributed and thus alter the intensity of impregnation of the underlying section. For these reasons it seems worth while to devise a method for adapting silver impregnation to paraffin sections, particularly to those fixed in Zenker's fluid. This has already been done in the case of formalin-fixed tissue in connection with

* From the Department of Pathology, University of Cincinnati College of Medicine.

1. Bailey, P., and Hiller, G.: J. Nerv. & Ment. Dis. **59**:337, 1924.

2. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926.

3. Mallory, F. B., and Wright, J. H.: Pathological Technique, ed. 8, Philadelphia, W. B. Saunders Company, 1924.

the Bielschowsky technic and fibrous reticulum by Maresch [4] (1905), Otani [5] (1927) and others; I have adapted it to Zenker-fixed tissue (Foot,[6] 1924).

Having succeded in that instance, I thought it desirable to experiment with the various methods set forth in the article by Bailey and Hiller and to attempt to adapt them to Zenker-fixed paraffin sections. While successful in the case of frozen sections, none of them appeared to be applicable immediately to that sort of material. Hortega's "fourth variant" of Achúcarro's silver tannate method showed promise of development but it had definite disadvantages; the strong tannic acid mordant acted on the egg albumin used to cement the sections to the slides, and the subsequent immersion of these in strongly ammoniacal solutions usually resulted in their detachment from the glass.

In further experiments with the method, it was found that reducing the percentage of tannic acid, increasing that of ammonium bromide and adding formalin to the mordant not only prevented this, but also improved the impregnation noticeably. Nerve fibers, both medullated and naked, became more sharply impregnated and the neuroglia showed a tendency to take on a respectable stain. It was also found that the length of time the sections remained in the mordant and the concentration of the silver bath were comparatively unimportant factors in the success of the impregnation; the ammonia wash that follows the mordant is the important element.

By introducing formalin into the tannic acid bath one apparently supplies a deficiency that has made the method unsatisfactory for use with paraffin sections. Frozen sections retain some formalin, but this is entirely removed by embedding in paraffin; it seems to combine reduction with impregnation, to a certain extent, before the final reduction with formalin is undertaken, and on this depends the success of the new method. The ammonia wash not only increases the flexibility and transparency of frozen sections; it also has its effect on the formalin they contain. For this reason, if I use the tannic acid mordant with formalin, in the case of paraffin sections, and then wash in the prescribed 10 drops of ammonia to 100 cc. of distilled water, I prolong the impregnation by restraining the action of formalin. By decreasing ammonia to 3 or 4 drops to 100 cc. of water, I accelerate the impregnation by imposing less restraint on the formalin; by omitting the ammonia entirely, I produce dark impregnation, not entirely free from precipitates. Thus one has a means of controlling the rapidity and intensity of impregnation and can emphasize one or other element in the tissues;

4. Maresch, R.: Centralbl. f. allg. Pathol. u. path. Anat. **16**:641, 1905.
5. Otani, S.: Am. J. Path. **3**:1, 1927.
6. Foot, N. C.: J. Lab. & Clin. Med. **9**:777, 1924.

Explanation of Figures

Fig. 1.—Nerve fibers in the region of the optic tract. Zenker fixation. This and the remaining photomicrographs were all taken with a 4 mm. dry lens. Magnification roughly 400 diameters.

Fig. 2.—Ganglion cells and fibers in an olivary nucleus. Zenker fixation.

Fig. 3.—Junction of granular and molecular layers of the cerebellum, with Purkinje cells and fine fibrils arborizing about them. Zenker fixation.

Fig. 4.—A Purkinje cell with part of its processes, demonstrating the effect of omiting the ammonia wash; over-impregnation should be noted. Zenker fixation.

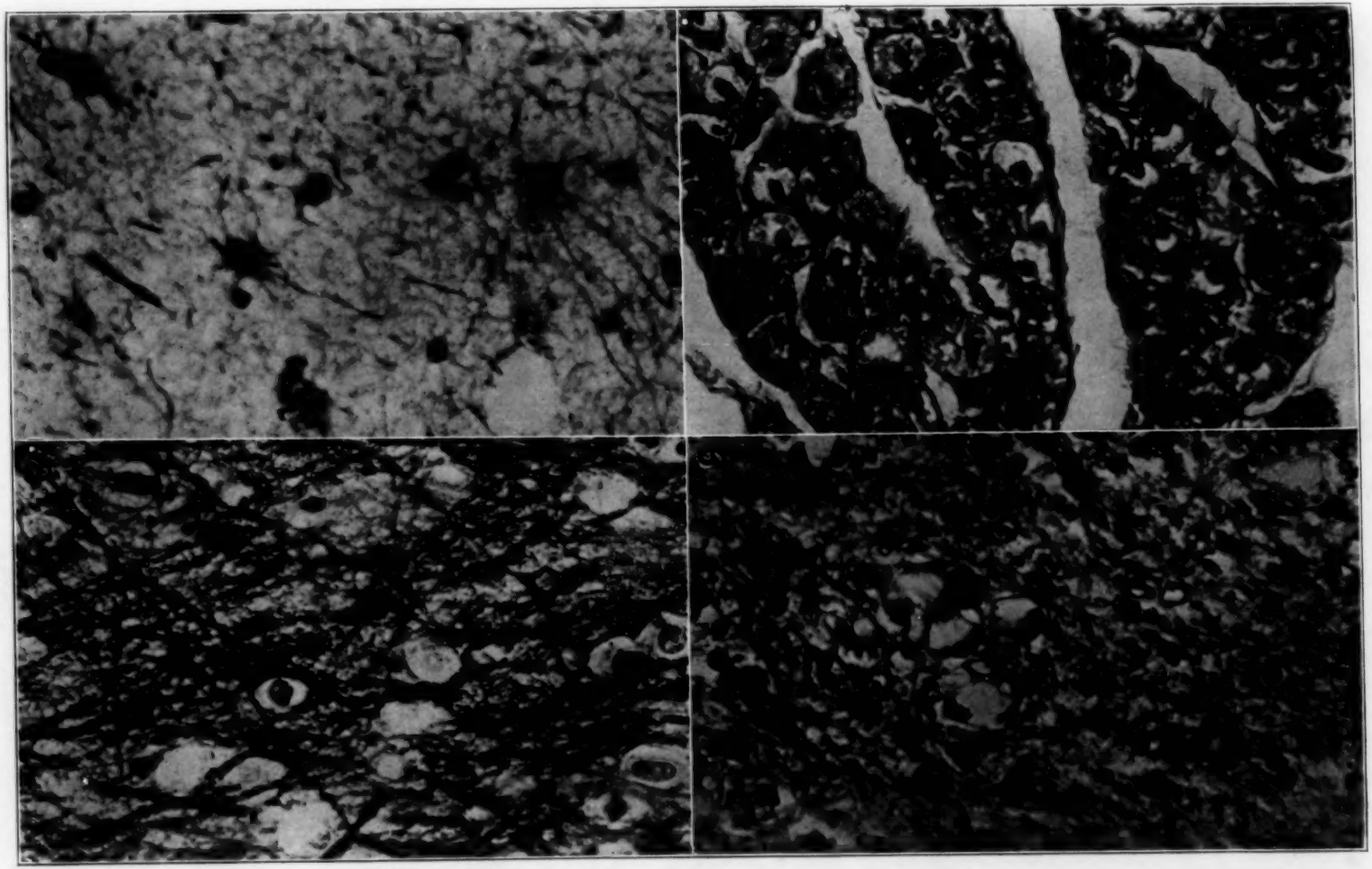
Explanation of Figures

Fig. 5.—Nerve trunks in dorsal root of cord; the axis cylinders and myelin sheaths are simultaneously stained. Zenker fixation.

Fig. 6.—Degeneration in anterior horn of cord in multiple sclerosis; phantoms of ganglion cells, vacuolization of nerves and faintly outlined astrocytes should be noted. Formalin fixation.

Fig. 7.—A group of astrocytes in the neuroglia capsule beneath the pia-arachnoid; the precision of neuroglia fibers with this impregnation should be noted. Ammonium bromide formalin fixation.

Fig. 8.—Heavy nerve fibers in deeper layer of cortex. Zenker fixation.



rapid impregnation brings out the nerve fibers and the astrocytes, slow impregnation improves the cytoplasmic detail in the ganglion cells and the neuroglia fibers are more precisely demonstrated.

As worked out by a process of trial and error, the best method for obtaining a good average impregnation is as follows:

Sections of Zenker-fixed material are cut at from 7 to 10 microns in paraffin and mounted as flatly and evenly as possible. If the dilute tannic acid mordant is used, sections as thick as 25 microns give splendid results; it is probable that even thicker sections may be successfully impregnated. The paraffin is removed with xylol and the sections run through alcohols of decreasing percentage into an alcoholic solution of iodine, the Zenker salts being removed as in Mallory's phosphotungstic acid hematoxylin technic.

The sections are treated for five minutes in a mahogany brown alcoholic solution of metallic iodine, washed at the tap and bleached in 5 per cent aqueous sodium thiosulphate. Then they are washed well and treated for five minutes in 0.25 per cent potassium permanganate and for ten minutes in 5 per cent oxalic acid (both aqueous) washing between. Next, they are washed well in water, followed up with a wash in distilled water.

The sections are then similar to formalin or formalin-bromide fixed tissue and are almost free from Zenker's fluid. From then on the procedure is alike for all three forms of fixation: all washes should be in distilled water; metallic instruments should not be used for handling the sections; the glassware should be scrupulously clean, and the solutions should be made up with distilled water.

Next, one is ready for the mordant. A stock solution is made up of pure tannic acid 0.15 parts, pure ammonium bromide 3.5 parts and distilled water 100 parts. This keeps fairly well and should be filtered if the tannic acid does not completely dissolve. This gives precise impregnations; if denser, browner results are desired, the tannic acid should be increased to 1.5 parts. To 95 cc. of this stock solution 5 cc. of 100 per cent neutral formalin (40 per cent formaldehyde) is added. This should be heated to 58 C. and poured slowly over the sections to avoid cracking the glass box or jar. The solution should then register from 50 to 55 C., owing to cooling. The sections should then be placed in an incubator for fifteen minutes at 37 C. The mordant does not keep well after formalin is added, so it should not be used for more than two sets of ten slides each.

After fifteen minutes in the mordant, the sections are washed immediately, while still warm, for thirty seconds in 100 cc. of distilled water to which 3 drops of strong ammonia have been added. The ammonia is then washed off with distilled water and the sections are impregnated for five minutes in a dilute silver-ammonium oxide solution, until they become an even brownish yellow; they are moved backward and forward with a glass rod to insure an even impregnation. This solution is made up as follows: To 10 cc. of 1 per cent aqueous silver nitrate add 1 drop of 40 per cent potassium or sodium hydroxide. The copious brown precipitate that forms is nearly dissolved in 4 or 5 drops of strong ammonia, care being exercised to leave a few grains of the precipitate out of solution. The solution is then diluted to 200 cc. with distilled water and used in two washes; as soon as the first becomes deep yellow, in about three minutes, it should be poured off and clean solution substituted.

After five minutes the sections should be properly impregnated. If they are too deep in color, the ammonia wash should be strengthened; if too pale, it should be weakened. One soon becomes acquainted with the proper depth of color and may be governed thereby, but it is better to regulate the ammonia wash so that five

minutes will give the desired results. The sections should be washed with distilled water and reduced in 20 per cent neutral formalin (8 per cent formaldehyde) for three minutes. They are washed in distilled or tap water and toned for three minutes in 1:500 gold chloride, whereupon they assume a deep purple brown. It is well to keep a stock solution of 1 per cent Merck's "brown, acid" gold chloride in distilled water and to make up fresh 1:500 solution from this for each day's batch of sections, discarding it after they are toned. It is often advantageous to dissolve 0.5 Gm. of mercuric chloride in 100 cc. of the toning bath, with the aid of heat, allowing the mixture to cool before it is used. This increases the precision of the impregnation in the dendrites of ganglion cells and in the neuroglia tissue and is of great value in improving the impregnation of sections fixed in Cajal's formalin-bromide solution. After they are toned the sections should be washed at the tap, fixed for three minutes in 5 per cent aqueous sodium thiosulphate and then washed well. They are then cleared and mounted in the usual way, through alcohol of increasing percentages into xylol and Canada balsam.

With this procedure, the nerve fibers are a rich violet or reddish brown, the smaller fibers possessing gemmules are black and the neuroglia fibers are yellowish brown. Ganglion cells are well impregnated, their processes standing out clearly, but finer dendrites do not become impregnated. The nuclei of all types are precisely stained and vary from brown to black. Fibrillary astrocytes may be readily identified, and their sucker feet are often well shown, but only the nuclei of other forms of neuroglia cells are clearly seen. The myelin sheaths and axis cylinders are simultaneously stained, as shown in one of the illustrations. In formalin, or bromide-formalin fixed tissue, the impregnation is paler, and the neuroglia are much more precisely stained. The bodies of the astrocytes are gray, rather than brown, as in the Zenker-fixed tissue. The reticulum of the meninges and vessels stains black, but the latter may be overstained. If a reticulum stain is desired, it is better to use a more specific method, although this impregnation gives suggestive pictures; the Bielschowsky-Maresch or the Hortega silver-carbonate methods are more precise.

SUMMARY AND COMMENT

Briefly outlined, the method is composed of the following steps:

1. Remove mercury and chromium salts from Zenker-fixed paraffin sections in the usual way.

2. Wash in distilled water and mordant in tannic acid bath for fifteen minutes at 37 C. after the mordant has been heated to 58 C.

3. Rinse for thirty seconds in weak ammonia water.

4. Wash briefly in distilled water and impregnate for five minutes in two changes of dilute silver-ammonium oxide, or until the sections are dark brownish yellow.

5. Wash in distilled water and reduce for three minutes in 20 per cent neutral formalin.

6. Wash and tone for three minutes in 1: 500 aqueous gold chloride.

7. Wash at the tap and fix for three minutes in 5 per cent sodium hyposulphite.

8. Wash well, and clear and dehydrate in alcohol, absolute alcohol and xylol, mounting in Canada balsam.

The accompanying photomicrographs, taken by Mr. J. B. Homan and me, will give a graphic presentation of the resuults of the method. The advantages of the procedure are as follows:

1. Shortness of time required to obtain finished sections; less than one hour is needed after they are affixed to the slides.

2. Flexibility of control; intensity is governed by the concentration of the ammonia wash, and various elements in the tissue are thus emphasized at will.

3. Applicability to Zenker-fixed paraffin sections.

4. General applicability to a number of elements of the nervous tissue at one time, which makes it a valuable routine method for the neuropathologist.

Other methods undoubtedly bring out the neuroglia cells to better advantage, but this procedure gives one a good idea of the general distribution and condition of a number of tissue elements at one time, demonstrates fibers prettily and brings out the details of the neuroglia capsule satisfactorily. Fibrillary astrocytes are especially well brought out. The other metallic impregnations mentioned in the article of Bailey and Hiller are now under consideration and attempts will be made to modify them for use with paraffin sections and Zenker-fixed material. In closing, it would be well to mention that formalin and formalin-bromide fixation work especially well with this silver tannate method; this point might be overlooked because of the emphasis laid on the Zenker fixation. The results with formalin material are paler, more precise in the neuroglia (particularly with the formalin-bromide fixation) and less monotone; the nerve fibers stain rather better in Zenker-fixed tissue.

General Review

THE RETICULO-ENDOTHELIAL SYSTEM

ITS RÔLE IN PATHOLOGIC CONDITIONS IN MAN *

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CHICAGO

CONTENTS

* From the Department of Pathology, College of Medicine, University of Illinois.

INTRODUCTION

Fourteen years have passed since the first publications of Aschoff, Landau and Kiyono on the reticulo-endothelial system. The progress accomplished by their work was not merely the clear definition of a certain type of mesenchymatous cells that had been recognized in part by previous investigators. Aschoff's and his co-workers' interest was from the very beginning chiefly concerned with the functional qualities of these cells. Their conception of the reticulo-endothelial cells has dominated many fields of histologic, experimental and clinical research during the last fourteen years. While some authors feel that the inclusion into one group of all the various cells of which the reticulo-endothelial system is composed lacks a sufficient background, the majority of investigators found the system a useful starting point for a great variety of observations.

The number of papers referring more or less directly to the reticulo-endothelium amounts today to nearly 500. Summarizing reviews of their contents have repeatedly been published in German (Aschoff, Schittenhelm, Boerner-Patzelt, Goedel and Standenath and Siegmund), as well as in English (Sacks) and in French (Oberling). After so much work has been done, the question seems to be justified as to what has been added to the knowledge of pathologic conditions in man, for after all a better understanding of the diseases in man is the ultimate aim of all our efforts. A separate consideration of the reticulo-endothelium in man is indicated the more since it is known that while these cells are present in all vertebrates down to the cyclostomes, they have their peculiarities in the different species of animals. It is from the standpoint of pathologic conditions in man that this review has been written.

DISTRIBUTION OF THE RETICULO-ENDOTHELIAL CELLS IN HUMAN BEINGS

The most reliable method to demonstrate the distribution of the reticulo-endothelium is the use of vital stains. Experiments on vital staining in man were carried out by Eppinger and Stöhr and by Ledofsky. They injected saccharated iron intravenously into moribund patients and found deposits of iron in the Kupffer cells of the liver and in the reticulo-endothelium of spleen, bone marrow and lymph glands. Ledofsky also mentions the occurrence of iron granules in the alveolar epithelium of the lung. The intensity of the iron storage seemed to be influenced by the underlying pathologic condition.

In carcinomatous patients who had been treated with injections of colloidal gold, I found that the metal was first deposited in the Kupffer cells of the liver. Shortly afterward it appeared in the reticulum and endothelial cells of the bone marrow and spleen and finally in the

reticulum of the abdominal lymph glands. Pictures resembling those seen in vitally stained animals can also be observed in patients that have died from malaria. The black granules of the malaria pigment bring out most distinctly the reticulo-endothelial cells of the hemopoietic organs. Some observers describe the malaria pigment also as taken up by the capillary endothelium of other organs, especially of the brain (Gaskell and Millar, Seyfarth, Dudgeon and Clark). Whether the capillary endothelium in general should be included in the reticulo-endothelium is still a matter of discussion. This question is complicated. Not only are there differences between the higher and the lower animals, but there exist also pathologic conditions, to be discussed later, in which the common capillary endothelium seems to assume qualities otherwise found only in the reticulo-endothelial cells.

In cases of the severe estivo-autumnal type of malaria most of the pigment in the capillaries of the brain is found enclosed in free, large mononuclear cells. Free pigment granules are also present and are often seen attached to the swollen and fatty degenerated endothelial cells which, however, do not engulf it. Granules of pigment finally may be taken up by enlarged adventitial cells about capillaries blockaded by large masses of pigment or by hyaline thrombi.[1] The malaria pigmentation of the intestinal villi is due to a storage of the black granules in adventitial and branched reticular cells. Similar observations have been described in intestinal melanosis from other causes (Hattori).

Another point of discussion is whether the reticulum cells of the thymus and the glia cells of the central nerve tissue should be classed with the reticulo-endothelium (Lubarsch, Aschoff). They store iron, fat and cellular débris, but are of ectodermic origin. In the thymus undergoing rapid involution, the cellular débris is engulfed by phagocytic cells apparently derived from the ectodermic reticulum (Ssyssojew). Recent studies by Popoff from Maximow's laboratory suggest, however, a different mode of origin of at least some of the phagocytic thymus cells. They are said to develop from the mesenchymatous adventitial cells of the smaller blood vessels.

All investigators agree that the Marchand's adventitial cells belong to the reticulo-endothelial system. These cells stand out distinctly in cases of nutritional disturbances of childhood in which they are filled with granules of iron (Lubarsch). They are present also in the testis, but have apparently no relation to the interstitial cells of Leydig.

Williamson and Pearse described an endothelial reticulum, which they compare with the Kupffer cells of the liver, lining the lymph spaces in the human thyroid and parathyroid. The accumulations of round cells commonly found in the suprarenal are, according to Paunz, derived from reticulo-endothelial cells. They are said to contain iron.

1. Unpublished.

J. Richter pointed out that the reticulo-endothelial cells are scanty in the female sex organs, an observation which does not agree with recent studies made by Hofbauer.

In several animals, such as the rabbit, mouse (M. B. Schmidt), and the *Macacus rhesus* (Krumbhaar and Musser), the removal of spleen causes a proliferation of the stellated cells of the liver. In human beings, Schmidt found only an enlargement, but no proliferation, of these cells following splenectomy.

RETICULO-ENDOTHELIUM AND BLOOD FORMATION

Granulopoesis.—Do the reticulo-endothelial cells in human beings give rise to the local formation of granulated blood cells, as has so often been described in animal experiments? The study of human material has the great disadvantage that one is usually dealing with far advanced changes which make difficult the exact determination of the histogenesis in cases of extramedullary blood formation. Even with regard to material obtained from animals, in which the conditions are so much more easily controlled, a great difference of opinion still exists. For a detailed discussion of this question I refer to the recent reviews by Herzog and Maximow. Aschoff states that in spite of many efforts he has not yet come to a definite conclusion. Vital staining, supravital staining and tissue culture still leave many problems unsolved (Maximow, Grossman, Sabin and Doan, Sabin, Lang).

Oeller, Siegmund and Domagk describe a transformation of adventitial and endothelial cells in immunized animals to granulocytes within a few minutes. Similar histologic pictures, however, occur spontaneously in the animals used in these experiments (Gerlach). They are seen especially in the lung, and are, I believe, remnants of old inflammatory processes. It is difficult to separate them from those supposed to take place within a few minutes.

In human beings such a rapid change in the character of the reticulo-endothelial cells has not been observed. It is not found in patients who die within a short time from acute infections (e. g., influenza) or in those who, in spite of the vaccination against typhoid, succumb to this infection.

Ssyssojew, examining the mesenteric lymph glands of children who had died from dysentery, found a large number of neutrophilic myelocytes in the glands. He follows Maximow in assuming the large lymphocytes to be the stem cells of this local myelopoesis. In acute infectious diseases, Herzenberg observed myeloid cells in the lymph glands, spleen and liver. She comes to the conclusion that these cells originate from the reticulo-endothelium. Previous studies on the occurrence of myelocytes in infectious tumors of the spleen were made by Hirschfeld.

In leukemia, Ferrata and his school described the appearance in the peripheral blood of a primitive blood cell, which he calls hemohistioblast. This cell has a delicate, basophilic cytoplasm and a round or oval nucleus with a peculiar, spongy chromatin structure. There are several distinct nucleoli. According to Ferrata, the hemohistioblast is identical with the reticulo-endothelial cells (clasmatocytes). It may differentiate to all forms of mature blood cells (Richter). It is beyond the scope of this review to go into greater detail of the extra-medullary blood formations in leukemia or pernicious anemia.

Regarding the erythropoesis, an observation of Peabody is quoted. This author found in regenerating human bone marrow a development of the erythroblasts from hypertrophic capillary endothelial cells.

Reticulo-Endothelium and Formation of Lymphocytes.—What has just been said about the granulopoesis holds true of the supposed development of lymphocytes from reticulo-endothelial cells. In spite of many studies (Hueck, Maximow), the differentiation of adventitial, reticular or endothelial cells to lymphocytes has not yet been definitely proved (Aschoff).

Petri found the development of red and white lymph glands in the retroperitoneal fat tissue in acute infectious disease. They originate from proliferating reticular and endothelial cells. First, the proliferating cells produce erythroblasts, myeloblasts and myelocytes; later, these areas become transformed to hemolymph glands, which are finally changed by removing of the blood to typical white lymph nodes. Petri's description reminds one of the formation of hemolymph glands in the fat tissue of sheep, reported many years ago by Warthin.

Relation of the Reticulo-Endothelial System to the Monocytes of the Blood.—The introduction of vital and supravital staining into the hematologic technic has again brought up a question which is as old as hematology itself, namely, that of the origin of the large mononuclear cells of the blood. Wollenberg, who devoted an article to the historical development of this question, found that the first to suggest an endothelial origin of the monocytes was Otto Tigri, in 1858. Mallory, in 1898, and Patella, in 1903, expressed the same opinion, and Mallory's term endothelial leukocyte is still often used.

Kiyono, Paschkis, Schittenhelm and Erhardt, Siegmund and Simpson described mononuclear cells containing granules of dye in the blood of animals that had been stained vitally. Although the number of these cells is small, this observation indicates that at least some of the mononuclear cells of the blood are derived from the reticulo-endothelial system. The dye-carrying cells are much more numerous in the right ventricle of the heart than they are in the left ventricle or in the peripheral circulation. Aschoff, Kiyono, Simpson and Siegmund suppose, therefore, that most of the vitally stained mononuclear cells given

off by the reticulo-endothelium of the spleen, liver and other organs are too large to pass the capillaries of the lung. They are kept back in the lung and either emigrate from the vessels or break down. Kiyono distinguishes three types of mononuclear cells in the rabbit's blood: histiogenic, myeloid and lymphogenic monocytes. Only the first type takes the vital stain.

Mononuclear cells, which on account of their content of phagocytosed material can be traced to the reticulo-endothelial system, have been observed in human blood under various pathologic conditions. The occurrence of malaria pigment in monocytes is well known (Naegeli, Seyfarth and others). Kawamura saw large blood cells filled with lipoid droplets in lipemic diabetes. Free macrophages containing erythrocytes and sometimes also leukocytes or their remnants were found in the blood of patients with malaria (Naegeli, Kartaschowa), relapsing fever (Kartaschowa), severe anemia (Malin, Rowley, Van Nuys), pernicious anemia after blood transfusion (Hopkins), sickle cell anemia (Sydenstricker, Huck, Cook and Meyer) and after splenectomy (Hoff, Domagk). Large phagocytic endothelioid blood cells were described in subacute bacterial endocarditis (Fontana, Hess, Hoff, Joseph, Kartaschowa, Sampson, Kerr and Simpson, Ottander, Schilling, Schittenhelm and Seyderhelm). In these diseases an intensive phagocytic activity of the fixed reticulo-endothelium is found. The probable origin of the large cells in malignant endocarditis will be discussed later.

Are these macrophages identical with or related to the monocytes of the normal blood? From morphologic studies of the cell structure, Petersen comes to the conclusion that the endothelial phagocytes are different from the monocytes and are rare in normal human blood. Sabin and Doan, using their method of supravital staining with neutral red and Janus green, found as a constant element in the human blood a type of cell which belonged to the general strain of endothelial derivates. These desquamated endothelial cells (clasmatocytes) are not related to the monocytes, and form from 3 to 4 per cent of the white blood cells. They are more common in rabbit's blood. The stem cell of the monocytes, however, is a primitive reticular cell occurring in greater numbers in organs like the lymph glands, spleen and bone marrow (Cunningham, Sabin and Doan). McJunkin differentiates three types of mononuclear blood cells: first, phagocytic cells giving a positive peroxidase reaction and staining supravitally with neutral red—there are the monocytes and they are formed in the bone marrow and spleen; second, lymph endotheliocytes which do not give the benzidine reaction stain supravitally with neutral red and which are derivates of the reticulo-endothelium of the lymph glands; third, hemoendotheliocytes, which give no reaction or only a weak one with neutral red, and which are negative for peroxidase—they probably arise from

the endothelium of the blood vessels, and occur in the blood of the rabbit, but are absent from normal human blood. Fontana distinguishes large or endothelioid histiocytes and small or lymphocytic histiocytes. A third type of histiocytes is found in leukemic blood.

According to Schilling, Masugi, Minerbi, Kohn, Holler, Rieu, Kaznelson and Bringeler, there is only one type of mononuclear cell which originates in the reticulo-endothelium. Wollenberg considers the entire vascular endothelium as producing monocytes. Schilling was not able to demonstrate an oxydase granulation in the monocytes. Similar observations were made by Schlenner, Bansi, Rosenthal and Wollenberg. If positive granules were present, they represented the remnants of phagocytosed granulocytes. Simpson and Schittenhelm and Erhardt obtained no oxydase reaction in rabbit's monocytes. On the other hand, Naegeli and Katsunuma consider that the monocytes are oxydase-positive and belong to the myeloid cells.

Evans called the large cells with a positive oxydase reaction, which he found in a case of syphilitic aortitis after injection of arsphenamine, "transitional cells." He considers these cells to be of myeloid origin. They develop independently, however, from the polymorphonuclear leukocytes.

This brief summary shows that the monocyte problem is still far from settled. From my own experience, I should say that the normal monocyte is derived from the reticulo-endothelium of the spleen, liver, bone marrow and lymph glands. I doubt whether much is gained by subdividing the large mononuclear cells of the blood. Differences between single cells may be due to their different ages and states of functional activity. Many of the monocytes contain a fine oxydase granulation which is different from that of the granulocytes. In severe infectious diseases, especially in those in which the skin is involved, capillary endothelial cells also may be present in the circulating blood. Their transformation to monocytes remains to be proved.

Monocytosis: The monocytes react independently from the other elements of the blood. For instance, in agranulocytosis, the monocytes may be increased (Schittenhelm, Gamna). Monocytosis is found in various diseases, in some of which there is histologic evidence of an abnormal stimulation of the reticulo-endothelium. I mention malaria (Ottander, Naegeli, Lucey, Meo-Columbo), kala azar (Krjukof), malta fever (Cathoire) and septicemia (Schilling).

In subacute bacterial endocarditis, monocytosis is frequently encountered (Bittorf, Fontana, Hess, Joseph, Kartaschowa, Kaznelson, Ottander, Schilling, Schittenhelm). Besides typical monocytes, large phagocytic cells are present. They resemble endothelial cells, may appear in groups attached to each other and often contain engulfed blood cells (Fontana, Joseph, Natousek, Simpson, Kerr and Simpson,

Ottander). Transitional stages between these endothelioid macrophages and typical monocytes were described by Joseph, Ottander, Schilling and others. Schilling, Hess and Joseph consider the cells a regular observation in malignant endocarditis. Fontana, however, pointed out that they are not seldom absent. Their temporary absence from the blood can be explained by the fact that they enter the blood in showers which are independent of temperature, pulse, or respiratory changes, time of day and digestion (Sampson, Kerr and Simpson). Kartaschowa saw similar cells in typhus exanthematicus, and Natousek observed them in cholera.

Bittorf, Fontana, Joseph and Ottander found that the endothelioid cells are most numerous in the first drop of blood taken from the ear after rubbing it. They believe that the cells are formed locally in distended capillaries and in small veins from proliferating endothelial cells. Schilling thinks that emboli composed of mobilized reticuloendothelial cells become lodged in the capillaries of the ear. He states that continuous rubbing causes a decrease of the cells. Hess agrees with him in this point, but emphasizes that the macrophages in malignant endocarditis arise from the vascular endothelium in general.

Abnormal mononuclear blood cells in large numbers are also observed in a mild acute infectious disease, the etiology of which is unknown. The disease is characterized by a febrile course, moderate enlargement of the lymph glands—especially those of the neck—inflammatory changes of the upper respiratory tract and a mononucleosis of the blood. Various names have been given to this disease, of which those most commonly used are: infectious mononucleosis (Baldrige, Rohner and Hansmann, Butka, Landon, Longcope, Mackey and Wakefield, Schenk and Pepper, Sprunt and Evans, White and others) and monocyte angina (Baader, Hopmann, Kwasniewski and Henning, Schulz and others). The nature of the abnormal mononuclear cells is still undecided. Some investigators, like Longcope, Sprunt and Evans, believe that they are of lymphocytic origin; however, they react to epinephrine differently from lymphocytes (Halzieyanu and Goia). In the German literature, they are usually classed with the monocytes. Hopman speaks of stem cells, and Kraswiewski and Henning suggest that both lymphocytes and monocytes may give rise to these cells. Other investigators want to use the term mononuclear cells without indicating their probable origin (Baldrige, Rohner and Hansmann). Histologic examination of the enlarged lymph glands reveals proliferation of the lymphoid cells as well as of the reticulum cells (Longcope, Baldrige, Rohner and Hansmann). It is therefore possible that both types of cells may enter the blood stream in abnormal numbers.

Monocytic Leukemia: The existence of a third type of leukemia was suggested by Reschad and Schilling. This third type of leukemia

is characterized by the appearance in the blood of immature, monocytoid cells and by an excessive proliferation of the reticulo-endothelial cells. Since Reschad and Schilling's first publication in 1913, similar observations have been reported by Hirschfeld, Bingel, Fleischmann, Reitano, Ewald and Richter. Schober and Opitz' case is doubtful. In some cases the immature and atypical monocytes were absent from the peripheral blood. Letterer speaks, therefore, of an aleukemic reticulosis. He describes an excessive proliferation of the reticulum cells in the spleen and lymph glands and a lesser proliferation in the bone marrow and liver. Borisowa, Pentmann, Goldschmid and Isaac observed an enormous systemic endothelial hyperplasia in the hemopoietic organs. The spleen, liver and bone marrow (Borisowa, and Goldschmid and Isaac) were involved, or the bone marrow was unchanged (Pentmann). Holler considers the Hodgkin's lymphogranuloma as an aleukemic reticulo-endotheliosis. This conception, however, has not been supported by other investigators.

While Ferrata and his school accept the monocytic leukemia as a hematologic entity, Naegeli believes that the monocytic type is nothing but a temporary initial variation of the myeloblast leukemia. Judging from the clinical and hematologic material at hand, there is, no doubt, much similarity between monocytic and acute myeloblast leukemia. Hoff explains the transformation of a monocytic leukemia into a myeloblast leukemia in the following way: In monocytic leukemia, an indifferent mesenchymatous tissue proliferates. If it remains in this indifferent stage, the leukemia does not change its character (stem cell leukemia—Ewald). If the immature mesenchyma develops, it produces myeloblast, and the monocytic leukemia passes into a myeloblast leukemia. There is much speculation to bring under one heading a number of rare and obscure conditions, some of which may be infectious in nature. As far as I can see, bacteriologic examinations have often been neglected in these cases. Sternberg pointed out recently that the whole group of monocytic leukemia still lacks a sufficient background. Krahn also doubts whether it is justifiable to speak of a new type of leukemia.

RETICULO-ENDOTHELIUM AND BLOOD DESTRUCTION

Phagocytosis of Erythrocytes.—Under normal conditions the worn-out erythrocytes break down in the circulating blood by fragmentation (Rous and Robertson, Krumbhaar, Doan and Sabin). In health, phagocytosis of red cells is insignificant. I have never found erythrocytes enclosed in reticulo-endothelial cells in normal human tissues. Under various pathologic conditions, however, these cells may display an intensive phagocytic activity. They often engulf enormous numbers of erythrocytes and their débris. The hemoglobin is transformed to granules of pigment and droplets, while the unstained stromas may

remain visible in the cells. But they too are finally destroyed. The reticulo-endothelial cells which line the vascular spaces are chiefly engaged in this process. The intensity with which they take part sometimes varies in the different organs.

There are two possibilities to explain the excessive phagocytosis of red cells by the reticulo-endothelium. Either there is an abnormal increase in the functional activity of these cells, or changes in the red cells themselves make them apt to become phagocytosed. The first possibility has been considered in connection with certain forms of anemia. Peabody and Broun lay great stress on the endothelial phagocytosis in pernicious anemia. Maliniu believes that the anemia in patients with carcinoma is due to an intensive erythrophagocytosis in the spleen. Naegeli thinks that in hemochromatosis the anemia results from an abnormal activity of the reticulo-endothelial system; but in hemochromatosis the anemia is usually mild.

Phagocytosis of erythrocytes has often been described in acute infectious diseases, especially in typhus exanthematicus (Aschoff, Gruber, Ceelen, von Prowaceck, Schmincke, Wolbach, Todd and Palfrey), Rocky Mountain spotted fever (Wilson and Chowning, LeCount, Wolbach), typhoid (Mallory, Graeff), paratyphoid (Sternberg) and malaria (Seyfarth). In Weil's disease, Lepehne found a peculiar fragmentation of the erythrocytes (erythrorhexis) in the reticulo-endothelial cells. Mallory suggests that the phagocytosis of erythrocytes in typhoid is due to a stimulation of the phagocytes by bacterial toxins. But it is much more likely that in infectious diseases the red cells that are engulfed are abnormal. The increased functional activity of the histiocytes is then not primary but secondary to an increased demand for removing the injured blood cells. Hektoen states that in certain infectious diseases, notably typhoid, the serum acquires the power to promote phagocytosis by its opsonic action on the red cells. The hemopsonins develop as a result of reactions in the infected body. Wright thinks of a toxic damage of the erythrocytes. To these explanations I may add another, namely, the adsorption of bacterial toxins through corpuscles of the blood (Starsky, Glusmann, Lintwareff). By destroying the erythrocytes laden with toxin, the macrophages eliminate the latter substances from the blood stream.

While in infectious diseases the whole reticulo-endothelial system is usually involved in the process of destruction of erythrocytes, in the hemolytic anemias the erythrophagocytosis shows a predilection for certain organs. It is striking that in pernicious anemia as well as in hemolytic jaundice the phagocytosis of red cells in the spleen is much less pronounced than it is in the other parts of the reticulo-endothelial system, although the spleen undoubtedly plays an important rôle in the pathogenesis of these diseases. The spleen is the organ that con-

tains the largest amount of reticulo-endothelial cells. Their action on the erythrocytes must, therefore, be other than by phagocytosis. It is possible that the splenic histiocytes excrete substances that dissolve the red cells or make them apt to become destroyed in the circulating blood or in other organs. In this connection I wish to describe observations which I have made in cases of sickle cell anemia. In this disease, which has so much in common with the hereditary hemolytic jaundice, there is little hemophagocytosis in the spleen. Histologic examination of the bone marrow reveals that the newly formed erythrocytes that leave the bone marrow appear morphologically normal. The spleen is packed with sickle cells. They are here much more numerous than in the circulating blood or in other organs; indeed, round erythrocytes are absent. One can see all the different stages of sickle formation. It is therefore probable that the transformation of the disk-shaped red cells to sickle cells takes place in the spleen under the influence of its reticulo-endothelium. The erythrocytes, no doubt, are of inferior quality from the very beginning. It is in the spleen that their weakness becomes manifest. The disfigured cells are finally phagocytosed by the reticulo-endothelial cells of the liver and of the abdominal lymph glands. Similar conditions may be present in the other forms of hemolytic anemias, although the action of the splenic histiocytes on the red blood corpuscles cannot be demonstrated by morphologic changes. From the histologic observations in the bone marrow in hemolytic jaundice, Helly concludes that in this disease the erythropoiesis is abnormal. On the other hand, it is known that the fragility of the erythrocytes is decreased after splenectomy (Krumbhaar).

In hemolytic jaundice, the Kupffer cells of the liver do most of the phagocytosis (Eppinger, Dick). In pernicious anemia large cells filled with erythrocytes and their débris were described in the bone marrow by Geelmuyden (1886) and Carnegie Dickson (1908). According to Peabody and Broun, the erythrophagocytosis is most extensive in the bone marrow. Doan determined the nature of the phagocytic cells in the bone marrow of pernicious anemia with the aid of supravital staining and found them to be of the type of endothelial macrophages or clasmatocytes, according to the terminology of Sabin, Cunningham and Doan. Fahr found much phagocytosis of red cells in the portal lymph glands and Eppinger in the Kupffer cells in cases of pernicious anemia.

Phagocytosis of Leukocytes and Blood Platelets.—In most of the diseases in which an intracellular destruction of erythrocytes occurs, phagocytosis is not restricted to these cells. The other elements of the blood are also taken up by the reticulo-endothelium and become dissolved. Their mode of breaking down, however, is less easily followed because the products of their disintegration are nonpigmented.

In myeloid leukemia I have sometimes found an intensive phagocytosis of the immature white blood cells by the Kupffer cells of the liver. The engulfing of granulocytes causes the Kupffer cells to become filled with oxydase granules. The positive oxydase reaction of the histiocytes observed in some leukemoid conditions (Ewald) may have a similar origin.

In granulation tissue phagocytosis of leukocytes by macrophages is constantly present. Maximow speaks of pus phagocytes. In the germinal centers of lymphatic tissue the reticulum cells often engulf the remnants of lymphocytes (Flemming's tingeable bodies). Toxic alterations of the lymph glands or of the malpighian bodies of the spleen sometimes leads to a complete replacement of the germinal centers by proliferating phagocytic reticulum cells (Groll and Krampf). The newer studies on the relations of the germinal centers to the formation and destruction of lymphocytes were recently discussed by Sternberg.

In some forms of thrombocytopenic purpura the underlying pathologic condition seems to be an abnormal destruction of blood platelets in the spleen. In these cases the removal of the spleen often means a complete cure of the condition, since the other reticulo-endothelial cells do not take over the abnormal function of this organ (Kaznelson, W. Mayo, Whipple, Brill and Rosenthal, Giffin and Holloway, and others [2]). Alrutz, Nortell and Piette described a phagocytosis of platelets by proliferating reticulo-endothelial cells in a case of thrombocytopenic purpura. Other investigators found only a piling up of the platelets in the sinuses of the spleen (W. Mayo, Kaznelson, Frank, Cori). Koster, from experimental studies on guinea-pigs, reaches the conclusion that phagocytosis by cells of the reticulo-endothelial system is not the only means by which the blood platelets are destroyed.

Von Prowazeck mentions the phagocytosis of platelets in typhus exanthematicus. Wolbach, however, could not confirm this observation.

Reticulo-Endothelium and Iron Metabolism.—The reticulo-endothelial cells store the iron that is liberated from disintegrated red blood cells. There are three different ways by which the iron may get into these cells: It may result from the intracellular digestion of phagocytosed erythrocytes; the riticulo-endothelial cells may take up the hemoglobin of cells dissolved in the circulating blood and transform it to hematin and iron pigment, or, finally, this transformation may take place in the plasma of the blood, and the histiocytes may resorb the ready iron (Aschoff).

The iron pigment that appears in the cells as dark brown granules is called hemosiderin (Neumann). This term is used only from a morphologic standpoint in order to characterize a certain kind of pig-

2. The case reported by Farley is a subleukemic acute myeloid leukemia. This explains the unfavorable result of the splenectomy.

ment which gives the microchemical reactions of iron. It yields no information as to its chemical nature, which is still unknown (H. G. Wells). Strasser thinks that it is iron oxide. Hueck supposes it to be colloidal iron free or loosely bound to protein or lipin substances. Little is known of the final disposition of this pigment. The body apparently tries to retain it, and several facts indicate that it is used over again for the formation of new hemoglobin (Wells, Aschoff). In this internal iron metabolism the reticulo-endothelial cells take an active part (Aschoff). Functional disturbances of the reticulo-endothelium lead to an increased excretion of iron with the urine (Eppinger, Kisch). For the relations between the spleen and the iron metabolism, I must refer to the reviews of Helly, Krumbhaar and Schmincke.

Chevallier distinguishes two types of iron cells. The first type is formed by parenchymatous cells, notably of the liver. This siderosis is the result of excretory processes (siderose parenchymateuse). The second type is composed of macrophages; these cells are most numerous in the spleen and liver. The iron they contain is used for assimilation (siderose d'assimilation). Chevallier calls these cells "siderocytes." Storage of trypan blue in the macrophages greatly impairs the assimilation of iron.

The difficulty sometimes encountered in the histochemical demonstration of iron in the tissues points toward the possibility that some of it may be deposited in a masked form. The histologic iron content, therefore, is not always identical with that determined by chemical methods. This problem is similar to the so-called fat phanerosis.

Apart from the deposits of iron derived from a local breaking down of red cells in hemorrhages and thrombi, hemosiderin is found under the following conditions:

Acute Infectious Diseases: Hemosiderin in the macrophages is observed especially in those infectious diseases which are characterized by erythrophagocytosis. The iron pigment usually appears in the later stages of the disease after the destruction of the red cells has reached its peak. I saw much hemosiderin in the liver and in the spleen of patients recovering from typhoid.

Severe Nutritional Disturbances: Chronic inanitious iron in the reticulo-endothelial cells was described by Aschoff, Lubarsch and Okuneff. This iron may be derived not only from red cells, but also from other disintegrating body cells. I observed much hemosiderin in the liver and spleen of people who had died from famine dropsy. Dubois found extensive hemosiderosis in atrophic infants. There was little erythrophagocytosis, and Dubois thinks there may be an intravascular hemolysis. According to Schwartz, Baer and Weiser, a mobilization of the iron metabolism is common in early infancy. Iron

pigment is present in liver and spleen. It disappears gradually after the third month. These authors trace the hemosiderin back to the hemorrhages that occur during birth. The piling up of iron granules in the reticulo-endothelial cells may interfere with their other functions, especially the formation of antibodies. Lubarsch says that iron pigmentation of the macrophages is common in the first year of life. He explains it on the basis of an abnormal permeability of the blood vessels. Schwartz, Baer and Weiser and Lubarsch apparently saw no relation between nutritional disturbances and hemosiderosis in infancy.

Hemolytic Anemias: It has already been stated that in the hemolytic anemias the phagocytosis of erythrocytes in the spleen is insignificant. Most of the investigators also agree that in pernicious anemias, the spleen contains no iron or only a little (Eppinger, Lubarsch, Schmidt, Schmorl, Sternberg). Similar observations were made in sickle cell anemia. Blood pigment is present only in and about trabecles, where it is derived from old hemorrhages (Graham, Sydenstricker, Hahn and Gillespie, Jaffé). In hemolytic jaundice, Dick did not find iron, and Rosenberg found little iron in the spleen. Eppinger and Weber had the same experience using Perl's Prussian blue method. When the sections were treated after Turnbull's method many granules of iron could be detected. Weber determined the chemical iron content of the spleen in hemolytic jaundice and found it higher than in leukemia. He had, however, no normal spleens with which to compare the condition.

Hemosiderosis is always marked in the liver. The Kupffer cells and the liver cells contain the iron. Sometimes the parenchymatous cells are chiefly affected; sometimes most of the iron is seen in the stellated cells. In seven cases of pernicious anemia, Fahr found the iron exclusively in the liver cells three times, mainly in the Kupffer cells once, and in both types of cells three times. Similar observations were made in hemolytic jaundice and sickle cell anemia (Dick, Rosenberg, Eppinger, Jaffé). Eppinger believes that only injured liver cells store the iron because they are unable to excrete it. Aschoff thinks that the duration of the elimination of iron determines the localization of iron in the liver. According to Rössle, the Kupffer cells transmit the pigment to the liver cells.

In pernicious anemia, Fahr described intensive hemosiderosis of the lymph glands around the hilum of the liver. The pigment cells in the bone marrow in pernicious anemia have long been known. In hemolytic jaundice iron pigment is found in the bone marrow. In the kidney, the iron is seen chiefly in the epithelial cells of the tubules.

Hemochromatosis: An enormous amount of iron-containing and iron-free blood pigment is observed in cases of hemochromatosis (von Recklinghausen). The iron pigment is deposited as coarse granules in the reticulo-endothelial cells, especially of the liver and the retro-

peritoneal lymph glands. The lymph glands are often compared to iron mines. Hemosiderin is also found in the parenchymatous cells of many organs (liver, pancreas, salivary gland, thyroid, parathyroid, and other organs) in the skin and in muscle fibers. The pigment that does not give the iron reaction is called hemofuscin. Mallory thinks that the hemofuscin becomes gradually transformed to hemosiderin. The spleen contains little pigment (Eppinger, Sprunt, March, Blanton and Healy, and others). Dunn speaks of abundant iron pigment only in the splenic phagocytes.

In spite of the extensive hemosiderosis, there are no signs of an increased blood destruction. The blood is either normal or shows a mild anemia which is much too insignificant to account for the enormous iron deposits (Eppinger, Howard and Stevens, Sprunt, March, Rouillard, Blanton and Healey, and others). Kühl suggests that in hemosiderosis an increased destruction of blood is present which is obscured by a prompt regeneration. The bone marrow, however, shows no signs of an increased functional activity (Dunn, Sprunt). Eppinger and Lubarsch try to explain the anatomic observations in hemochromatosis on the basis of a functional insufficiency of the reticulo-endothelial cells (siderocytes). Because these cells are unable to take care of the iron liberated from the blood at a normal rate, it accumulates in the organ and is finally also stored in the glandular cells and muscle fibers. What prevents the histiocytes from transporting the iron to the bone marrow? Is it a chronic poisoning with small amounts of copper (Mallory)? If the histiocytes do not perform their normal duties in carrying the iron to the places of formation of blood, would we not expect a severe anemia even if there is no abnormal destruction of blood? What rôle does the liver play? Has the cirrhosis something to do with the retention of the iron in the body? In looking over the literature on hemosiderosis, one finds more questions than positive statements. A good summary of the opinions expressed by English and French investigators is found in the discussion on hemochromatosis at the eighty-ninth meeting of the British Medical Association and in a recent article by Rouillard.

There are a number of other diseases in which hemosiderosis is observed. In scurvy and leukemia the iron pigment in the reticulo-endothelial cells arises no doubt from the hemorrhages. I have often seen much hemosiderin in the cervical, thoracic and retroperitoneal lymph glands after transfusion of blood, although the blood of the donors seemed to be compatible according to the usual laboratory tests.

Reticulo-Endothelium and Formation of Bile Pigment.—During recent years much material has accumulated suggesting a formation of the bile pigment in places other than in the liver cells (Aschoff, Brulé, Elek, Eppinger, Kálló, Kodama, Lepehne, Mann and associates,

McNee, Makino, Rich, Rich and Rienhoff, Whipple and Hooper). The only function which the liver cells are said to have in connection with the bilirubin is to excrete it, thus securing its constant level in the blood (Aschoff, Brulé, Eppinger, Lepehne, Makino, Rich). Some investigators, however, still believe in the conception of Minkowsky and Naunyn that it is only the liver cell that forms the bilirubin (Bieling and Isaac, Lubarsch, Kanner, Melchior, Fischer, Rosenthal and Licht, Retzlaff, Heinrichsdorff, Greppi).

The bilirubin is derived from the hemoglobin. Since the reticulo-endothelial cells are so closely connected with the destruction of blood, it seems probable that these cells also produce the bile pigment (Aschoff and his school, Eppinger, Rich, and others). The transformation of the hemoglobin to bilirubin may take place in the histiocytes or in the circulating blood. In the latter case, it is likely that the ferments which split up the hemoglobin molecule are given off by the reticulo-endothelial cells (Aschoff, Lepehne).

The reticulo-endothelial cells are widely distributed in the body. It is therefore to be expected that bilirubin may be formed from hemoglobin anywhere in the tissues. The presence of bilirubin in old hematomas has been repeatedly demonstrated (Makino and others). Rich described the intracellular formation of hematoidin (bilirubin) crystals in small hemorrhages of the leptomeningi.

In birds, the liver and in particular the Kupffer cells are the chief producers of the bile pigment. The same seems to hold true for the mammals under normal conditions (Rich). Mann, Sheard and Bolleman, however, came to the conclusion that all but a small amount of bilirubin is made outside the abdominal cavity, namely, in the bone marrow. What is formed in the liver and spleen is insignificant. It is difficult to conform their opinion with the observations of Oppenheimer and of McNee and Prusik. These authors obtained no increase of the pigment content in the blood of extremities in which the vessels had been tied off immediately after inducing hemolysis. The experiments of Rich also point toward the great importance of the abdominal viscera for the formation of bilirubin.

Histologic studies of jaundice in man yield interesting observations which, however, are sometimes difficult to explain on the basis of the conception just mentioned. Thus, bile pigment in the Kupffer cells is constantly present only in cases of mechanical (dynamic) icterus. This pigment is phagocytosed, as is evident from its structure. It appears often as casts of the intercellular bile capillaries. Kanner believes that the phagocytosis of the bile pigment by the Kupffer cells is stimulated by an increase of the cholesterol in the plasma.

In the cases in which the jaundice results from an abnormal destruction of red cells (productive icterus of Aschoff), bilirubin is usually

absent from the Kupffer cells of the liver and from the reticulo-endothelial cells of spleen, bone marrow and lymph glands. Kuczynski found nodules of proliferating and destroying Kupffer cells in the liver of a syphilitic patient who had developed a severe icterus after injections of arsphenamine. Besides engulfed red cells, the macrophages contained granules of iron and a green pigment. But these conditions are rare. They are not seen in hemolytic jaundice, sickle cell anemia or pernicious anemia. One is therefore compelled to assume that the histiocytes excrete the bile pigment as soon as it is formed, thus preventing its intracellular accumulation in demonstrable amounts, or that the final transformation of the iron-free part of the hemoglobin occurs in the blood.

The abnormal destruction of red blood corpuscles is, however, not always accompanied by jaundice. In typhus and typhoid, jaundice is not common, although the erythrophagocytosis in these diseases is most intensive. Lepehne emphasizes the mode of destruction of erythrocytes. For instance, in infectious jaundice (Weill's disease), the red cells engulfed by histiocytes break up into hemoglobin droplets. This erythrorhexis takes place mainly in the spleen and to a lesser degree in the liver, bone marrow and lymph glands. In infectious diseases without jaundice the intracellular fragmentation of the red cells is not found. There is only phagocytosis of the whole cells. If icterus occurs in septicemia, typhoid or similar conditions, the destroying histiocytes show the same picture as in Weill's disease. Weill described a case of pulmonary tuberculosis with jaundice in which macrophages containing droplets of hemoglobin were seen in the peripheral blood stream. The intracellular breaking up of the erythrocytes cannot be an absolute requirement for the formation of bilirubin by macrophages, since it is not found in hemolytic jaundice or in sickle cell anemia.

There is still another question. The liver can take care of much larger quantities of bilirubin than it does normally (Tarchanoff, Makino). Why does it not compensate the increase of bilirubin in the blood in hemolytic anemias, slight as it may be, as in pernicious anemia? In hemolytic jaundice, the liver cells appear normal (Aschoff). But does this mean that their function is normal? Lepehne finally admits that the liver parenchyma may also be altered in Weill's disease.

The physiologic icterus of the new-born is hemolytic in nature. The pathogenesis of the severe, pernicious form varies. In some cases there are signs of injury in liver cells (Klemperer). Other forms are due to an abnormal toxic destruction of erythrocytes. Lepehne described two cases of erythrorhexis seen in infectious jaundice. Klemperer made a similar observation. Schmincke does not mention this form of intracellular destruction of red cells. He found enlargement of the Kupffer cells with erythrophagocytosis, lysis of the red cells and accumulation of iron granules and bile pigment in the macrophages.

The microscopic picture of the spleen also indicated an anhepatocellular origin of the icterus. Stolz studied the liver of a child, aged 4 days, whose mother had been suffering from subacute yellow atrophy of the liver at the time it was born. The Kupffer cells were filled with bile pigment, which Stolz believes had been phagocytosed.

I saw recently the organs of a child that had developed an intensive jaundice twenty days after it was born. It died a few days later. It was one of the rare cases of severe familial icterus in earliest infancy. The only other child of the family had succumbed previously to the same condition. The splenic pulp was filled with myeloblasts. There were many macrophages packed with erythrocyte débris. Numerous cells also contained droplets of iron pigment. In the liver intercellular bile thrombi and granules of bile pigment in the parenchymatous cells were found. This pigment appeared deep greenish brown. It was also present as casts and granules in the huge Kupffer cells. There was no erythrophagocytosis. The portal capillaries showed a large number of myeloid cells.

Jaundice is sometimes observed in myocardial insufficiency. According to Fishberg, this jaundice is due to an increased destruction of stagnating erythrocytes by reticulo-endothelial cells. Fishberg's conclusions are merely theoretical, since in these cases there is no abnormal erythrophagocytosis.

RETICULO-ENDOTHELIUM AND LIPIN METABOLISM

Fat Storage in Histiocytes Resulting from Local Destruction of Tissue and Resorption of Fat.—The reticulo-endothelial cells have a great affinity for lipoids, especially for cholesterol esters. In cases of destruction of tissue these cells often store the fat set free from the disintegrating cells and become thus transformed to large, foamy, mononucleated and multinucleated cells, the cytoplasm of which is filled with anisotropic lipoid droplets. Other cells, too, such as capillary endothelial cells, fibroblasts and even epithelial cells, may undergo a similar transformation, but the majority of the pseudoxanthomatous cells, as Aschoff calls them, are derived from the local histiocytes. This can be demonstrated by their vital staining (Anitschkoff).

The pseudoxanthomatous cells are observed in the pyogenetic membranes of old abscesses, in the wall of pus tubes, in the stroma of the large white kidney, in the alveoli of lungs with gelatinous pneumonia, in atheromatous plaques of the aorta, in chronic mastitis, and in certain tumors and granulomas. For a detailed description of these changes, I refer to the recent publications of Schridde, Stewart, Seyler and Kirch.

The infiltration of the mucosa of the gallbladder with cholesterol-filled macrophages leads to the macroscopic picture of the so-called strawberry gallbladder (Moynihan, MacCarty, Stewart, Herxheimer,

Boyd). According to Aschoff and Bacmeister, the cholesterol stored in the wall is reabsorbed from the bile. Stewart thinks that the strawberry gallbladder is the local manifestation of a hypercholesterinemia and is comparable to the xanthoma of the skin.

Blumgart described a peculiar, fatal disease, resembling sprue, which he explained on the basis of a disturbed resorption of fat in the intestine. In the mucosa of the small intestine he found small granulomas composed of macrophages filled with fat. Similar fat phagocytes also were present in the mesenteric lymph glands.

Fat Storage in Histiocytes Resulting from Disturbances of the Lipin Metabolism.—The accumulation of lipoids in the histiocytes is not always due to the local resorption of fat. There are instances in which these changes are manifestations of a disturbed fat metabolism.

Xanthomatosis: Well known examples of such disturbances are the xanthomas (xanthelasmas—Aschoff) of the skin. The bright yellow plaques and nodules contain chiefly large cells filled with double refracting cholesterol compounds. Chauffard and Laroche, in 1910, were the first to show that the cholesterol deposits in the superficial layers of the cutis result from a hypercholesterinemia. Xanthomas are therefore most commonly found in diseases which lead to an increase of the blood cholesterol, such as diabetes mellitus, obstructive icterus and chronic glomerulonephritis. Major studied three cases of diabetic xanthoma showing lipemia and hypercholesterinemia. After insulin treatment, the lipemia and hypercholesterinemia disappeared. Regarding the influence of the insulin on the xanthomas, Major says that the resorption of the cholesterol deposits in the skin depends partly on the disappearance of the lipoidemia and partly on the degree of blood supply which permits the resorption of the substances in the lesions of the skin.

There are also cases of idiopathic xanthomatosis in which the cause of the hypercholesterinemia cannot be determined (Yamakawa and Kashiwara). Pautrier and Lévy observed three cases of xanthomatous tumors with marked hypercholesterinemia in one family. It is not surprising that the blood cholesterol is not always high in persons with xanthomas of the skin (Rosenthal and Braunstein). The increase of the cholesterol may have disappeared by the time the sample of blood is taken. Stewart mentions that the xanthomas sometimes outlast for a long time the hypercholesterinemia that has produced them.

Finally, it may be said that the localization of the xanthomatous plaques in the skin may be determined by a mechanical irritation. More information about these lesions can be obtained in the publications of Harrison and Whitfield, Stewart, Hoffmann and Fahr.

Among the reticulo-endothelial cells of the internal organs, the Kupffer cells of the liver show the greatest tendency to store fat. Fat is just as common in these cells as it is in the liver cells. There is,

however, no relation between these two cells regarding their lipoid content (Fischer). From the literature at hand, I was not able to obtain any information as to what might cause this frequent fatty infiltration of the stellated cells. It is likely that the fat which they contain is taken up from the blood. An agonal mobilization of body fats perhaps plays an important rôle. In future studies on the fatty infiltration of the Kupffer cells special attention should be given to the lipin content of the blood before death.

The most marked steatosis of the Kupffer cells is observed in diabetes (Roessle, Fischer, and others). It is clear that the blood is the source of the lipoids in these cases.

Lipemic Diabetes: Diabetic lipemia may also cause the storage of lipoids in the histiocytes of the spleen. The occurrence of fat-containing cells in the spleen is rather common (Schmincke, Kusunoki), but the changes are most marked in diabetes. In the milder cases the fat accumulates in and about the malpighian bodies. It is located in cells with a foamy cytoplasm or in elements resembling fat cells. Free fat droplets are often seen. They may be derived from broken-down fat cells, or may represent fat that has been deposited without being taken up by histiocytes. According to the staining reactions, the fat is a mixture of neutral fat, cholesterol esters and phospholipins. The latter are usually predominating.

Extreme lipoid infiltration of the splenic reticulo-endothelial cells produces a characteristic macroscopic appearance of this organ. The spleen is distinctly enlarged, soft, without structure and bright brick-red. The pulp consists almost entirely of large foam cells crowded with fat that stains black by the method of Lorrain Smith. Often granules and droplets of neutral fat or cholesterol esters are also present. The chemical composition of the stored lipins varies in the different cases. These changes of the spleen in lipemic diabetes were described by Lutz, Marchand, Oppenheim and Fishberg, Schöndorff, Schultze, Smith, Warren and Root, William and Dresbach. I can add another case from my own material which has not been published, that of a man, aged 56, who died in diabetic coma. The spleen weighed 280 Gm.; the pulp was soft and light brick-red. The reticulum and endothelial cells had assumed the shape of large, round bodies stuffed with fat droplets which did not stain with sudan III and nile blue sulphate, but took the Lorrain Smith and Caccio stain. Single cells were filled with neutral fat. Scattered between the fat phagocytes were a few lymphoid cells and plasma cells which were free from lipoid material. The Kupffer cells of the liver contained only neutral fat and cholesterol esters and were only slightly enlarged. The large cells were also absent from the other organs of the reticulo-endothelial system. Some investigators found them in the bone marrow (Marchand) and in the

liver (Smith, William and Dresbach), but they were less numerous there than in the spleen. That diabetic lipemia does not always lead to such a storage of fat in the splenic histiocytes is evident from the observations of Eppinger and Hübschmann.

Niemann's Disease: Peculiar, severe disturbances of the lipin metabolism occur in infancy and in earliest childhood, in which the spleen shows changes similar to those observed in lipemic diabetes. The infiltration of the macrophages with lipoid material is, however, much more generalized than it is in diabetes. The reticulo-endothelial cells of the spleen, bone marrow and lymph glands, the adventitial cells (clasmatocytes) of the loose connective tissue, the Kupffer cells of the liver and the reticulum cells of the thymus are all involved. The cells are also present in the mucosa of the small intestine and in the capillaries of internal organs (lung, kidney, pancreas). They are not found in the peripheral blood (Schiff), because they are apparently too large to get into the peripheral blood vessels (Bloom). In the older literature these cases have sometimes been misinterpreted as infantile forms of Gaucher's disease. Pick emphasizes that there is no relation between these two conditions, and suggests the name lipoid splenohepatomegaly (Niemann's disease). Bloom wants to substitute the term lipoid histiocytosis (type Niemann). Niemann was the first to call attention to this rare disease. Fahr and Stamm suggest relations with the xanthomas. Puncture of the spleen and demonstration of the lipoid phagocytes in the splenic fluid makes a diagnosis in vivo possible (Bloom, Schiff, Hamburger). Further observations are necessary to prove that this is a definite and independent type of disease.

Gaucher's Disease: When Gaucher in 1882 reported his observation of a peculiar tumor of the spleen, he called it a primitive epithelioma. Since his publication, about sixty cases of the disease which now is named for him, have been described. Many of these cases were recently reviewed by Cushing and Stout and, in particular, by Pick. Recent years have brought much information regarding the histiogenesis and the chemistry of the cells typical of this disease.

The occurrence of the Gaucher cells is limited to the hemopoietic organs. They are most numerous in the spleen, and are also found in the liver, lymph glands and bone marrow. Pick assumes that the disease starts in all these organs simultaneously, but that during the course, the spleen usually becomes most affected. Sometimes the changes of the bones are pronounced (Risel, Pick, Cushing and Stout).

The cells develop from the reticulum cells and from the adventitial cells of the arterioles and capillaries (Risel, Mandelbaum and Downey, Kraus, Pick). According to Pick, the endothelial cells are not involved. The cytoplasm of the Gaucher cells appears wrinkled and rumpled (chiffonée, zerknittert). Between the wavy protoplasmatic fibrils is

deposited a substance that stains pale blue with Mallory's aniline blue method. Lieb and Epstein found that this substance contained large quantities of a cerebroside which by its physical and chemical properties could be determined as kerasin. Cushing and Stout mention that Dr. Bauman, using Lieb's method, obtained from a dried Gaucher spleen 16 per cent of a crude cerebroside.

The reticulum cells that have been transformed to Gaucher cells are still able to engulf blood cells. They often contain hemosiderin. Epstein even found hematoidin in the cells.

The etiology of Gaucher's disease is unknown. Schlangenhaufer emphasized the familial occurrence. Epstein noted it in 36.6 per cent of his cases. Waugh and MacIntosh call it a primary, perhaps familial, aleukemic dysmyelosis. The next step leading to the final explanation of this disease would be to find out whether the Gaucher substance is stored by the reticulum cells or formed by them. In the latter case, Gaucher's disease would be a true primary disease of the reticulum cells. It also remains to be shown why the endothelial cells are not affected. Weil and Chevallier, struck by Carrel's method of the culture of an invisible virus in macrophages, cannot help but believe that such a virus may infect the reticulum cells in Gaucher's disease and cause its tumor-like alteration.

The lipemic splenomegaly, Niemann's disease and Gaucher's disease have been grouped together as "storage diseases." Epstein's term, "lipoid histiocytomatosis," is a linguistic monster that will hardly be generally accepted.

RETICULO-ENDOTHELIUM, PROTEIN METABOLISM AND CARBOHYDRATE METABOLISM

The storage and intracellular transformation of proteins by the reticulo-endothelial cells so far have not been demonstrated. This is chiefly due to the fact that there are no methods at hand which allow a differentiation of stored proteins from the cell proteins proper. Siegmund thinks that the granules and vacuoles observed in histiocytes after the injection of foreign proteins indicate such a storage. The same author also explains the increase in plasma proteins that follows the injection of foreign proteins, colloidal metals and acid vital stains by their stimulating action on the reticulo-endothelium.

Demant's experiments indicate that the reticulo-endothelial system takes part in the carbohydrate metabolism. He observed in fasting dogs a distinct increase of the blood sugar after intravenous injection of colloidal silver, which is readily stored by the reticulo-endothelial cells.

The only carbohydrate which can be detected by microscopic methods is glycogen. The histiocytes are indifferent to the glycogen; at least, they do not store it. In patients with diabetes, who had been under insulin

treatment for a long period of time, I found much glycogen in the form of casts and granules in the lymph spaces about the portal capillaries of the liver. The granules were often attached to Kupffer cells, which, however, did not phagocyte it. The presence of the glycogen in the lymph spaces would not prevent its storage by the Kupffer cells, since these cells take up bile, vital stains and other material from the lymph vessels.

RETICULO-ENDOTHELIUM AND WATER METABOLISM

Jochweds investigated the influence of intravenous injection of colloidal silver on the elimination of water. He observed that the storage of the silver in the reticulo-endothelial cells decreased and delayed the excretion of water. In patients with a tendency to retention of water, the colloidal silver intensified the tendency. Jochweds sees in his experiments an additional proof for the extrarenal origin of the retention of water. Similar observations were made by Paunz.

Saxl and Donath suggest that the hormones act on the water metabolism by way of the reticulo-endothelial system. Thus, thyroid extract makes these cells more permeable, while pituitary extract and insulin decrease their permeability.

RETICULO-ENDOTHELIUM IN PREGNANCY

Benda concludes from the increased permeability of the meninges during the second half of the pregnancy that there is an alteration of the entire reticulo-endothelial system during gestation. This alteration leads to fatty degeneration and necrosis of the endothelium in cases of toxemia and eclampsia. Lundwall observed a more rapid storage of congo red by the reticulo-endothelial cells in pregnant women than in nonpregnant women. In eclampsia, Domagk described swelling, proliferation and fatty degeneration of the capillary endothelium in the liver, lungs and kidneys. In the spleen there were also signs of an activation of the histiocytes. It appears from these observations that in eclampsia the changes involve the entire vascular endothelium and not only the specific endothelium of the hemopoietic organs. Hofbauer found that during pregnancy a phagocytic tissue develops in the broad ligaments, which is most extensive after prolonged labor. He points out the great importance of the local accumulation of macrophages for the resistance against infections. The macrophages develop from adventitial cells. Hofbauer's studies confirm the earlier observations of Hornung.

RETICULO-ENDOTHELIUM AND INTERNAL SECRETION

The beneficial effect of the extirpation of one suprarenal in polyglobulia induced Stephan to assume an inhibitory influence of the suprarenal hormones on the reticulo-endothelial system. He explains

pernicious anemia on the base of an abnormal function of the reticulo-endothelial cells, which can be checked by increasing the output of these hormones. He saw some improvement in cases of pernicious anemia following the intraperitoneal implantation of pieces of a suprarenal. The reticulo-endothelial system, according to the same author, is the most important defense mechanism against malignant tumors. The activity of the histiocytes, therefore, should be stimulated in patients with tumors. To accomplish that Stephan suggests the surgical removal of one suprarenal. The changes that he described in the cortex of the suprarenals in cases of carcinoma, however, are not typical of this disease.

In connection with Stephan's considerations, I may mention an observation of Willmore and Douglas showing extensive degeneration of the histiocytes in a case of suprarenal tumor.

With the aid of a method to be described later, Saxl and Donath found an increased activity of the reticulo-endothelium in exophthalmic goiter.

RETICULO-ENDOTHELIUM AND INFECTIONS

Numerous observations indicate the intimate connection of the reticulo-endothelial cells with the defense reactions of the body against infections. Since more is known about these cells, the origin of most of the immune bodies has been traced to them. Thus, immunity, not long ago a humoral question, once more becomes a cellular question, as first advocated by Metschnikoff (Besredka).

Space does not permit me to take up the rôle of the histiocytes in inflammation, their relation to the other inflammatory cells and the question of their mutual transformation. The studies of Metschnikoff, Marchand and Maximow in this field belong to the classics of medicine. Much interesting information can also be obtained from the recent publications of Roessle, Herzog, Kuczynski, Oeller and Siegmund. The great importance of the macrophages for the local immunity has been thoroughly discussed by Gay.

The following functions have been attributed to the reticulo-endothelial cells in connection with infections: first, the phagocytosis and intracellular destruction of the micro-organisms; second, the reception, detoxication and digestion of the waste products that are formed during the process of inflammation, including the toxic substances liberated from the bacteria; third, the absorption of soluble toxins; and fourth, the secretion of the antibodies (bacterio-lysins, agglutinins, antitoxins, and other bodies).

Phagocytosis and Host Cells.—Among the free cells of an exudate, the polymorphonuclear leukocytes (microphages) are much more active than the macrophages (Metschnikoff). If, however, the bacteria enter

the blood stream and get in contact with the fixed histiocytes, they later become their worst enemies (Wyssokowitsch). The macrophagocytosis is therefore of a greater biologic value than the microphagocytosis (Singer). In immunized animals the phagocytosis of the bacteria by the reticulo-endothelial cells is greatly hastened and intensified (Domagk, Siegmund, Jacob, Adler and Singer). By the perfusing method, Manwaring and Fritschen found that spleen and liver have the greatest affinity to bacteria.

In infectious diseases in man the phagocytosis of pathogenic micro-organisms by the reticulo-endothelium of the internal organs is much less distinct than it is in the artificial infections of animals. In natural infections the bacteria usually enter the blood stream gradually, and the activity of the histiocytes, therefore, extends over a much longer period of time than in animals injected with bacteria. When in certain diseases the macrophages contain large numbers of bacteria or protozoa, it is often difficult to decide whether the phagocytosis means the destruction of the micro-organisms or whether the macrophages act as hosts. This question has been raised especially in connection with the chronic granulomas which contain enormous numbers of intracellular parasites (Mueller). In leprosy, Babes called the relation between the hypertrophic macrophages (Virchow's leprosy cells) and the bacilli a true symbiosis. But in old lesions the bacilli gradually disappeared from these cells (Herxheimer). Marschalkó gives a similar explanation for the Mikulicz cells in rhinoscleroma, which are large histiocytes stuffed with capsulated bacilli.

Cunningham, Sabin, Sugiyana and Kindwall say with regard to the phagocytosis of tubercle bacilli by monocytes that these cells usually fail to destroy them and that the number of bacilli which can be seen within an individual cell point to the idea that the bacilli multiply within the cell. They suggest, therefore, that the tubercle bacilli live as parasites within the monocytes. There are many forms of tuberculosis in man, however, in which tubercle bacilli are scanty. Besides, the morphologic changes of the bacilli in the epithelioid cells of tubercles in man are difficult to explain other than by their gradual disintegration.

Paltauf used to say that the large cells of the lymphogranuloma looked like host cells. Kuczyniski and Hauk found inclusions in the Sternberg-Reed cells which they considered as fungi. While Sternberg denies the etiologic significance of these structures, Barron suggests that they may be animal parasites or reactions to them.

In typhus exanthematicus and Rocky Mountain spotted fever, *Rickettsia* were found in enlarged endothelial cells by Kuczynski and Wolbach, Todd and Palfey. Wolbach and his associates demonstrated the tiny coccoid bodies especially in the lesions of the skin, then in the brain, kidneys and testes. The fact that they were also present

in the muscle fibers of the vessels points to their active invasion into the cells, since muscle fibers do not perform phagocytosis.

Leishmaniosis is a specific disease of the reticulo-endothelial cells (Letulle, France, Girand and Caudiere). Large numbers of parasites fill the swollen histiocytes. They show no signs of disintegration, and the histiocytes seem to be entirely passive.

Resorption of Waste Products, Antibody Formation and Adsorption of Toxins.—The resorptive functions of the reticulo-endothelial cells in infections are suggested by their swelling and by their increased affinity for basic stains resulting from an increased acidity of the cytoplasm. The formation of vacuoles in the cytoplasm can be explained on the same basis (Kuczynsky, Siegmund). The adsorption of toxins and the production of antibodies are indicated by the results of experimental studies. Pathologic conditions in man offer no direct information. The most important of these experiments deal with the depressing or stimulating action of the so-called blockade of the reticulo-endothelial cells with vital stains or colloidal metals (Adler and Singer, Bass, Freund, Gay and Clark, Howell, Jungeblut and Berlot, Kobayashi and Schiwotsu, Ledingham, Meyer, Neufeld and Meyer, Standenath, Stewart and Parker, Vannucci and others). It is impossible to speak of a complete elimination of the entire reticulo-endothelial system by these crude methods. This is shown by the negative results of Warschatowa and Leontieff, Weiss and Kunze, Fraenkel and Gruneberg and Louros and Schayer. However, if the injections are given over a sufficient length of time and are combined with a removal of the spleen, there can be no doubt that the storing of the dye or metal interferes with the formation of antibodies.

Metschnikoff, Kobzarenko, Stenstroenn and Petterson investigated the problem of whether the macrophages are able to fix soluble toxins in vitro. The results of their investigations were negative or doubtful. They used suspensions of macrophages obtained by the injections of blood cells or egg albumin. These macrophages cannot be considered normal. The adsorption of toxins can be demonstrated, however, when the fixed macrophages are tested in situ (Bieling and Gotschalk).

Reticulo-Endothelium in Typhoid and in Septicemia.—The most marked reaction of the reticulo-endothelial cells is found in typhoid and in cases of paratyphoid B resembling typhoid (Mallory, Graeff, Jaffé, Faber, Mestitz, Sternberg). The proliferating histiocytes are active phagocytes. They engulf blood cells and cellular debris, but do not contain bacteria. The experience with typhoid vaccination indicates that the endotoxins of the bacilli stimulate the histiocytes (Askanazy). The absence of the bacilli from the areas of cellular proliferation also suggests an excretion of bacteriolytic substances by these cells. The

cases of typhoid without anatomic lesions are perhaps due to a lack of reactivity of the reticulo-endothelial cells. They are, however, not always fatal, especially in children.

In unchecked streptococcus infections there is, according to Siegmund, no mobilization of the Kupffer cells of the liver. Kuczynski found a swelling and proliferation of the Kupffer cells in septicemia. These changes are considered by Siegmund as signs of reactive and immunizing processes. The cellular activation is, however, not restricted to the reticulo-endothelial cells, but affects the entire capillary endothelium, so that under the influence of the infection the differences between the specific endothelium of the hemopoietic organs and the common endothelium disappear (Siegmund). Hence, in subacute bacterial endocarditis the proliferation, desquamation and phagocytosis of the endothelium also is observed in the capillaries of the skin (Bittorf, Hess, Siegmund, Ottander). The generalized activation of the capillary endothelial cells also may account for their phagocytosis of bacteria in the skin, which has been described by Mallory and Medlar in measles, by Bruusgaard and Thjotta in gonococci meningitis, by Harbitz in pneumococcic infections and by Thomson and Wulff in epidemic meningitis. Polymorphonuclear leukocytes in the lumen of the capillaries may also contain the meningococci (Pick, Bendar, Gruber and Kerschensteiner).

In pyemia, puerperal sepsis and acute miliary tuberculosis, Siegmund observed the formation of intima granulomas in the smaller blood vessels of the liver, spleen, lung, bone marrow and skin and in the endocardium. They result from the local destruction of micro-organisms by macrophages, followed by thrombosis and organization.

Exhaustion of the active mesenchyma causes necrotic inflammations, as they occur in influenza, agranulocytosis and in infections complicating leukemia (Siegmund). It has been repeatedly shown that in leukemia the antibody formation is also diminished (Moreschi, Rotky and Howell). A severe alteration of the reticulo-endothelium has been noted by Wail in relapsing fever.

Specific Granulomas.—Histiocytes are the essential morphologic elements in many specific granulomas, especially in leprosy (Choma and Gayo, Herxheimer, Oliver), granuloma inguinale (Goldzieher and Peck), rhinoscleroma (Mallory, Marschalkó), sporotrichosis (D'Agata), Delhi boil (Letulle), blastomycosis and other types. In syphilitic lesions the occurrence of histiocytes is less significant. The histiogenesis of the tuberculous epithelioid cells has caused much interest. Maximow has pointed out that the action of the tubercle bacillus is a specific formative stimulation to which the histiocytes (resting wandering cells) and lymphocytes are particularly sensitive. Aschoff questions whether the conclusions drawn from animal experiments should be applied to

tuberculosis in man. In tuberculous lesions in man, the fibroblastic reactions may be more pronounced than the proliferation of the histiocytes. Doan and Sabin state that the epithelioid cells and giant cells of tuberculous lymph glands in man are positive to the peroxydase reaction. The fine blue granules correspond to the reaction in some of the monocytes. The epithelioid cells of lymphogranuloma are similar to those of tuberculosis (Doan and Sabin). McJunkin traces the Sternberg-Reed cells to the reticulum cells. Piney calls Hodgkin's disease a reticulo-endotheliosis.

A hyperplasia of the reticulo-endothelial cells, with the formation of nodules composed of large phagocytic cells in the spleen, liver, bones, lymph glands, myocardium and pancreas, has been described by Schultz, Warmbter and Puhl. The etiology of this disease remained unknown. A similar case has been reported by Thompson, Kegan and Dunn.

Finally, the large phagocytic cells of the malakoplakia are mentioned as derived from the adventitial cells (Landsteiner and Stoerk).

RETICULO-ENDOTHELIUM AND MALIGNANT TUMORS

Relations between Reticulo-Endothelium and Tumors in General.—The experiments that led Edwin Goldmann to the discovery of the pyrrhol cells were undertaken with the intention of influencing the growth of malignant tumors. His studies were unfortunately ended by his early death from a malignant new-growth. Neudorfer suggested that the reticulo-endothelial cells are important in preventing metastases. Similar conclusions can be drawn from the investigations of Lazarus, Barlow and Parry on the resistance of the spleen against grafts of Jenner's sarcoma. Erdmann, on the other hand, showed that an irritation (or blocking?) of the reticulo-endothelial cells with India ink makes possible a transplantation of tumors by killed tumor cells or tumor filtrates.

The experiences with tumors in man, at the first glance, lend no support to the theory that resistance against tumors depends on the histiocytes. It is true that metastases to the spleen are rare. They are common, however, in the other organs of the reticulo-endothelial system, especially in liver and lymph glands. In carcinoma of the breast a marked proliferation of the sinus endothelium is frequently found in the axillary lymph glands. This proliferation is present also in cases in which the primary tumor is still small and shows no necrosis or ulceration. One considers these changes due to chronic inflammation. I have found that in the glands with an intensive new formation and desquamation of the endothelial cells, metastases are usually absent, while they are found when the endothelium shows no reaction. May

I suggest that the proliferation of the endothelium is a defense reaction against tumor cells carried to the glands with the lymph stream?

Tumors of Reticulo-Endothelial Cells.—Rous' sarcoma of the chicken, is, according to Carrel, composed of monocytes (macrophages). The virus of the Rous' tumor has a specific affinity to the macrophages in which it can be cultivated.

Tumors consisting of monocytes have so far not been reported in man. There are, however, tumors that originate from the fixed reticulo-endothelial cells. Hemangio-endotheliomas of the liver were described by Fischer, Loehlein, Kothny, Kahle, Hachfeld and Goedel. Malignant tumors of the spleen derived from the reticulum and endothelial cells were published by Risel, Bunting, Foix and Roemmele. Ewing traces certain multiple or systemic tumors of the lymph glands to the reticulum and endothelium. The cases of Caccio, Parlavecchio and Goedel belong to the same group. Piney speaks of a reticulo-endothelioma. Connor explains the endothelial myeloma of the long bones (Ewing tumor) as reticulum cell tumors of the bone marrow. Frazer calls the mycosis fungoides a reticulum cell sarcoma of the skin.

Von Gaza injected lithion carmine and trypan blue into a polymorpho-cell sarcoma of the tibia. He obtained vital staining of the macrophages and fibroblasts. The tumor cells did not take the vital stain. He also found that only the dead tumor cells were phagocytosed by macrophages.

FUNCTION TESTS OF RETICULO-ENDOTHELIAL SYSTEM

The functional activity of the reticulo-endothelium has been tested by the intravenous injection of substances that are stored in the histiocytes and by determining the time which is required until these substances have disappeared from the blood.

Intravenous injection of congo red and colorimetric determination of the dye in the serum after four and sixty minutes has been recommended by Adler and Reimann. They found retention of the dye in cases of septicemia, in diseases of the liver and in circulatory disturbances. Congo red is harmless and has been used repeatedly for determining the volume of blood and for detecting an amyloid degeneration during life. It is, however, not a good vital stain. Judging from my experience, better results can be obtained by the procedure of Saxl and Donath. These authors injected intravenously a fine emulsion of oil. The granules of this emulsion are so fine that they pass through the smallest capillaries. The injections cause no reactions, and the blood picture does not change. The disappearance of the granules is studied by dark-field examination of droplets of blood taken from the finger. Saxl and Donath saw an increased activity of the reticulo-endothelium

in exophthalmic goiter and a decreased activity in cirrhosis of the liver, septicemia and uremia.

Little attention has been given so far to the possibility that the reticulo-endothelial cells may store substances injected for the purpose of determining the function of certain organs, especially of the liver. Maurer and Gatewood consider such a possibility, and Saxl and Donath demonstrated that a preceding injection of colloidal silver causes a retardation of the excretion of phenoltetrachlorphthalein.

ATTEMPTS TO INFLUENCE THERAPEUTICALLY THE RETICULO-ENDOTHELIAL SYSTEM IN DISEASES

Attempts to influence therapeutically the reticulo-endothelial system in diseases can be divided into two groups. The first group includes the efforts to decrease the function of the histiocytes. In the second group, a stimulation of these cells is intended.

Decrease of Function of Reticulo-Endothelium.—Reduction of Functionating Tissue: The main method is the extirpation of the spleen, which contains the largest number of histiocytes. This operation has often been used in the diseases with an increased destruction of blood. The best results are obtained in hemolytic jaundice. Some improvement also may be observed in pernicious anemia and in sickle cell anemia. But these diseases are not cured by the splenectomy. What is accomplished is the elimination of the large control station for the insufficient red blood cells. If it is eliminated, the destruction of blood will be diminished, at least temporarily. The quality of the blood cells, however, will not improve. The principal changes are located in the bone marrow. Even if the spleen should exert an inhibitory action on the marrow, the removal of this depressing action would not transform an insufficient bone marrow into a normal one. It also has to be kept in mind that sooner or later other parts of the reticulo-endothelial system may take over the function of the spleen, and the improvement will be only temporary.

The value of splenectomy in thrombocytopenic purpura has already been discussed.

Blockade Therapy: The blocking of the reticulo-endothelial cells by intravenous injections of colloidal metals has been recommended by Fischer and Kirch in hemolytic anemia and by Hollaender in pernicious anemia. Saxl and Donath thought that by a preceding blockade of the histiocytes with colloidal silver certain drugs may be kept longer in the circulating blood. I think that such a blocking of the reticulo-endothelial apparatus cannot be considered seriously. I may say that at least 10 cc. of colloidal silver per kilogram are required to obtain something approximating a temporary blockade of all the histiocytes. Who would

risk injecting 1,000 cc. of colloidal silver into a patient? Small amounts will only stimulate these cells.

Sometimes the storage of the colloidal metal by the reticulo-endothelial cells may prevent the action of this metal on other cells of the body. This has recently been shown in the colloidal lead treatment of patients with malignant tumors (Martland and von Sochocky). The lead is deposited in the histiocytes of the spleen, liver and bone marrow, while it cannot be demonstrated morphologically in the tumor. I had the same experience five years ago with colloidal gold.

In this connection the observation on the relations between arsphenamine and reticulo-endothelium may be quoted. A storage of the arsphenamine by these cells has been reported by Schlossberger. Memmesheimer and Kloevekorn speak of a depressing action of the arsphenamine on the histiocytes. Del Baere had a similar experience.

Increase of Function of Reticulo-Endothelium.—The stimulating effect of colloidal substances on the mesenchyma manifests itself mainly in an activation of the histiocytes. If the intensity of the vital staining is considered an index of the functional activity of the reticulo-endothelial cells (Goldmann, Kiyono, Siegmund, and others), this stimulating effect can be demonstrated after the injection of various colloidal substances, especially proteins (Nissen, Pentimalli, Siegmund). Thus, nonspecific protein therapy affects first the histiocytes, which are the most irritable fixed cells of the mesenchyma. Later, the activation may spread over the entire vascular endothelium.

Stephan mentions that acriflavine influences the function of insufficient reticulo-endothelial cells. After the injection of colloidal silver, Nissen found an intensified myelopoiesis in the bone marrow. Kraft recommended injections of saccharated iron to stimulate the formation of blood after hemorrhages.

Another method to stimulate the histiocytes is the exposure to the roentgen ray. Intensified vital staining after radiation has been described by Schmidt and Holtermann, and others. Soper says that weak dosages of the roentgen ray stimulate, and large dosages paralyze, the histiocytes. Stephan, Neddermeyer and others saw an increased coagulability of the blood after irradiating the spleen. Deep roentgen-ray therapy has therefore been recommended in cases of hemorrhages from various causes. Stephan advances the theory that if the right dosage is used, the roentgen ray causes an increased secretion of prothrombin by the reticulum cells. Another explanation for the hastening of the clotting of blood after irradiation of the spleen is given by Neddermeyer. He suggests that the rays induce an increased destruction of the blood platelets in the spleen, and that it is from the breaking down of platelets that thrombokinetic substances are liberated. Hence, the

platelet count decreases. Exposure to the mercury vapor quartz light perhaps has a similar effect on the blood coagulation (Sooy and Moise). Warthin and Case described intensive phagocytosis in an abdominal lymphosarcoma after roentgen-ray irradiation. That insoluble products of radium and mesothorium are stored by the reticulo-endothelium has been observed by Martland, Conlon and Knef.

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Notes and News

University News, Promotions, Resignations, Appointments and Elections.—At the last meeting of the Association of American Physicians, A. S. Warthin was elected president. Dr. Warthin has been reelected first vice president of the American College of Physicians and editor of the *Annals of Clinical Medicine,* and recently was elected president of the American Association for Cancer Research.

N. M. Popoff has been appointed pathologist and director of the laboratory at Highland Hospital, Rochester, N. Y., in the place of Ralph H. Mellon.

Shields Warren has assumed charge of the pathologic work in the Palmer Memorial Hospital in Boston, a new hospital for cancer closely allied with the Deaconess Hospital.

Ralph H. Mellon has accepted the directorship of the laboratory of the Western Pennsylvania Hospital at Pittsburgh.

At the University of Pennsylvania, the department of pathology has been placed under the chairmanship of Eugene L. Opie, who will continue as director of the laboratory at the Phipps Institute; E. B. Krumbhaar has resigned as director of laboratories of the Philadelphia General Hospital to assume the professorship of pathology left vacant by the death of Allen J. Smith; Herbert Fox has become professor of comparative pathology, and Baldwin Lucké has been promoted to associate professorship. Joseph MacFarland is professor of pathology; Morton McCutcheon, assistant professor of pathology; Stuart Mudd, assistant professor of experimental pathology, and Damaso Rivas, assistant professor of parasitology.

Eduard Kaufmann, professor and director of the pathologic institute at the University of Göttingen, was retired from official duties on April 1, 1927. He was professor in Basel from 1898 to 1906, when he came to Göttingen as successor to Borst. His "Lehrbuch der speziellen pathologischen Anatomie," which has gone through several editions, is well known.

Laboratory for Study of Rocky Mountain Spotted Fever.—A state laboratory for the study of Rocky Mountain spotted fever is to be erected at Hamilton, Mont., and an appropriation of $25,000 a year for the next biennium has been made for reasearch on this disease. The state board of entomology, in cooperation with the U. S. Public Health Service, is in charge of this work.

Jewish Laws Regarding Postmortem Examinations.—Jewish law does not prohibit postmortem examinations when good reasons exist for performing them. In fact, the Talmud stipulates that if the examination may result in the saving of a human life, it is not only justifiable but desirable. If these facts were brought to the attention of the Jewish people, a great deal of opposition to autopsies would be overcome.—Julius Gottlieb, *Boston M. & S. J.* **196**:726, 1927.

Autopsies on Jews and Gentiles.—"As a step forward in securing autopsies among Jews I believe that every Jewish doctor should arrange that a post mortem examination should be made upon himself at his death and that one should take especial pains in the families of Jewish physicians to secure permission for these examinations. These same suggestions I would make to Gentile doctors and their families. Only by means like these will prejudices be overcome."—Elliott P. Joslin, *Boston M. & S. J.* **196**:728, 1927.

National Research Council Fellowships in Medicine.—At a meeting of the medical fellowship board on April 30, 1927, the following fellows were reappointed:

Leopold R. Cerecedo, biochemistry, L. B. Mendel, Yale University.
Martin H. Dawson, pathology, Rufus I. Cole, Rockefeller Institute for Medical Research.
Peter Heinbecker, physiology, Joseph Erlanger, Washington University.
Francis F. Heyroth, chemistry, Theodore Svedberg, Upsala.
Ralph G. Smith, pharmacology, Arthur L. Tatum, University of Chicago.
Willard O. Thompson, biochemistry, Lawrence Y. Henderson, Harvard University.

The following fellows were appointed:

Walter Bauer (M.D., Univ. Mich.), internal medicine, H. H. Dale, London.
Detlev W. Bronk (Ph.D., Univ. Mich.), physiology, E. D. Adrian, Cambridge University.
Arda A. Green (M.D., Johns Hopkins), biochemistry.
Haldan K. Hartline (M.D., Johns Hopkins), physiology, A. H. Pfund and R. N. Wood, Johns Hopkins University.
Thomas D. Jones (M.D., Univ. Va.), internal medicine, Sir Thomas Lewis, University College, London.
John F. Kessel (Ph.D., Univ. Cal.), parasitology, R. W. Hegner and W. W. Cort, Johns Hopkins University.
Robert M. Moore (M.D., Wash. Univ.), physiology, W. B. Cannon, Harvard University.
Paul W. O. Preisler (Ph.D., Wash. Univ.), biochemistry, William M. Clark, U. S. Hygienic Laboratory, Washington, D. C.
Francis O. Schmitt (Ph.D., Wash. Univ.), physiology, G. N. Lewis, University of California.
Vincent duVigneaud (Ph.D., Univ. Rochester), biochemistry, John J. Abel, Johns Hopkins University.
Lester R. Whitaker (M.D., Harvard), surgery, Harvey Cushing, Harvard Medical School.

Death of E. A. Homén.—Ernst Alexander Homén, professor of pathologic anatomy in the University of Helsingfors, Finland, from 1886 until recently, has died at the age of 75. Homén was a stimulating teacher and an industrious and productive worker, and his institute was an active center of investigation. Not less than thirty candidates took their doctor's degree under his direction. He and his pupils made important contributions to pathology, particularly on infections of the nervous system, as illustrated especially by their work on the effects of streptococci in the nervous system and on epidemic poliomyelitis (Wickman). Owing to an unusual arrangement, Homén had command of a small number of beds, which he used to excellent advantage for the thorough study of valuable clinical cases. The reports from Homén's institute were published in a stately series under the title "Arbeiten aus dem pathologisch-anatomischen Institut der Universität Helsingfors."

Abstracts from Current Literature

Pathologic Physiology

THE RELATIONSHIP OF OBESITY TO CARBOHYDRATE METABOLISM. HENRY J. JOHN, Am. J. M. Sc. **173**:184, 1927.

Reports of twelve cases of obesity, three in males and nine in females, are presented, in each of which the carbohydrate metabolism was studied by means of a dextrose tolerance test. The overweight in these cases ranged from 29 to 115 per cent. Glycosuria was present in two cases in both of which diabetes was present. The fasting blood sugar was normal in eleven cases, among which four were cases of diabetes of varying degrees of severity. Among the twelve cases of obesity, two were definitely cases of diabetes; three were cases of mild diabetes or "prediabetics."

AUTHOR'S SUMMARY.

EXPERIMENTAL GANGRENE PRODUCED BY DIETARY MEANS. ARTHUR H. SMITH and MAXWELL BOGIN, Am. J. Path. **3**:67, 1927.

A number of rats, on a limited calorie dietary regimen, developed dry gangrene of the tail. Apparently a method has been found for the experimental production of a form of gangrene due to nutritional disturbances.

THE RELATION OF MENSTRUATION TO THE PERMEABILITY OF THE SKIN CAPILLARIES AND THE AUTONOMIC TONUS OF THE SKIN VESSELS. W. F. PETERSEN and G. MILLES, Arch. Int. Med. **38**:730, 1926.

There is a change in capillary permeability preceding and during menstruation. Schroder, by means of local constriction, was able to determine capillary hemorrhages in the skin, from two to eight days before menstruation but not at the onset of menstruation. The authors found that in the premenstrual period the capillaries are more permeable and that changes take place in the autonomic innervation of the arterioles, whereby the skin region becomes parasympathetic and the visceral area presumably sympathetic. There may be a slight increase of the metabolic rate at this time, although the evidence is conflicting (thyroid hyperfunction). If so, it does not affect the temperature of the normal woman because the skin can readily dissipate heat. Menstruation represents a biologic rearrangement evidently involving an ionic change and an endocrine change, as well as an alteration in the autonomic nervous apparatus. The three forming the vegetative control of the tissues are the fundamental factors in the reaction of the organism to infection. In menstruation the alteration, associated with an increased permeability of the capillaries and tissues, makes for less favorable conditions of resistance to tuberculosis. In the broad sense, the menstrual cycle can be termed one of vagotonia. Examination by means of the blister method showed that the normal rate of permeability for skin capillaries is approximately 0.72 for the intermenstrual period, 0.75 for the premenstrual and 0.77 for the menstrual. In the premenstrual period the skin tonus is parasympathetic; this seems to be reversed promptly with the onset of menstruation. In the premenstrual and menstrual period the blood pressure average is higher than during the intermenstrual period.

S. A. LEVINSON.

THE GROWTH OF THE BONES IN CHILDHOOD. H. A. HARRIS, Arch. Int. Med. **38**:785, 1926.

The author confirms the views of Hunter with regard to growth in length of the long bones in nonrachitic children. The author's valuable contribution on this subject may be summarized as follows: Transverse striations are shown to be manifestations of cessation of growth. They occur normally in adolescence; they may occur with seasonal variations in the rate of growth; they occur in all cases of marked decrease in rate of growth from any form of acute illness or starvation; they occur as part of the healing process in rickets. The skeletal processes are analyzed in terms of (1) the area of cartilage proliferation, (2) cartilage calcification and degeneration and (3) ossification proper. These three areas are related to (1) a water soluble growth promoting vitamin or vitamins, (2) the enzyme of Robison, or vitamin X, and (3) the fat soluble vitamin A proper. These processes are discussed in terms of the archusia or growth promoting principle, and the ergusia or differentiating principle of Burrows, as enunciated for results obtained from cultures of normal and pathologic tissues. A rational basis is suggested for the analysis of the processes involved in diseases of cartilage and bone, applicable to all ages. The term "growth promoting" as commonly applied to vitamin A is a misnomer. The growth promoting vitamins are water soluble.

S. A. LEVINSON.

DIET AND TISSUE GROWTH: IV. THE RATE OF COMPENSATORY RENAL ENLARGEMENT AFTER UNILATERAL NEPHRECTOMY IN THE WHITE RAT. ARTHUR H. SMITH and T. S. MOISE, J. Exper. Med. **45**:263, 1927.

The rate of compensatory enlargement of the remaining kidney, after unilateral nephrectomy, has been studied in adult rats fed diets containing various concentrations of protein. A curve of enlargement on "standard" food (18 per cent casein) shows a rapid initial increase, with subsequent slower rise to the one hundred twentieth day. There is not any significant difference between the value at 120 days (44 per cent) and that at 150 days (48 per cent). A similar series with diets containing increasing concentrations of proteins but with a constant time interval (twenty-one days) after nephrectomy shows an increase in the degree of enlargement directly proportional to the protein content of the food. The values vary from 24 per cent with the 18 per cent casein ration to 77 per cent with the 90 per cent casein diet. A third series shows the enlargement on "high protein" food (85 per cent casein). The values vary from 49 per cent at three days to 121 per cent at 150 days. There is not any significant difference between the value at 120 days (123 per cent) and that at 150 days (121 per cent). Determinations of total solids on the experimental kidneys show that the recorded enlargement involves mainly an actual tissue increase.

AUTHORS' SUMMARY.

THE RELATION OF THE HYPOPHYSIS TO DIABETES MELLITUS. A. R. COLWELL, Medicine **6**:1, 1927.

The rôle of the hypophysis in carbohydrate metabolism is not definite with certainty at present. It is probable that it is without significance in this field as a gland of internal secretion, but important nerve centers or pathways are situated in or near it which are concerned in the control of the metabolism of carbohydrates. It is not impossible that these centers or tracts are involved in the control of the insulin secretion.

AUTHOR'S SUMMARY.

A Case of Prolonged Lactation in an Algerian Woman. L. Ceard, Arch. de l'Inst. Pasteur d'Algérie **4**:93, 1926.

The article gives the analysis of the milk of a woman, about 60 years old, who was nursing her grandchild.

A Further Observation on Interrenalism. E. Mathias and E. Petzal, Klin. Wchnschr. **5**:2313, 1926.

Interrenalism is a name for the complex of influences exerted by pathologic changes of the suprarenal glands on the body form and the sexual characteristics of the patient. In a woman, aged 32, a hypernephroma metastasized to the orbit, the maxillary sinus and the ethmoid. It caused marked hypertrichosis of the face, atrophy of the uterus and the mammae, cessation of menstruation and progressive masculine changes of the escutcheon and of the facial expression.

J. D. Willems.

The Influence of Ultraviolet Rays on the C-Vitamin Content of Cow's Milk. P. Reyher, Klin. Wchnschr. **5**:2341, 1926.

The antiscorbutic principle in cow's milk is destroyed by ultraviolet rays. Thus, rickets is not so much a light deficiency disease as a nutritional disturbance.

J. D. Willems.

Investigations on the Ovarian Hormone in the Blood of Gravid and Non-gravid Women. E. Fels, Klin. Wchnschr. **5**:2349, 1926.

Subcutaneous injection of a substance containing ovarian hormone is known to produce specific changes in the secretion and the epithelium of the vagina of the mouse. This method demonstrates the presence of ovarian hormone in the blood of women in the third trimester of pregnancy; also its absence in non-pregnant women and those in early pregnancy.

J. D. Willems.

A Contribution to the Question of Pubertas Praecox. E. Stransky, Klin. Wchnschr. **5**:2358, 1926.

In a female child with primary hypergenitalism menstruation began in the second year; the secondary sex characteristics, bone development and body form and growth are far in advance of the child's age.

J. D. Willems.

The Influence of Roentgen Rays on the Acid Base Equilibrium. C. von Pannewitz, Strahlentherapie **24**:327, 1926.

This is a brief report of extensive investigations of the changes in the acid base equilibrium of rabbits and human beings following roentgen-ray exposure. The urine did not show any appreciable fluctuation in the H-ion concentration. The reaction of the blood appeared in two phases; directly after the treatment there was a slight acidosis which turned into alkalosis from two to five hours later. The degree depended on the part exposed; an increasing scale from extremities, ovaries and uterus, thorax and abdomen was noted. The first phase is believed to be due to a direct roentgen-ray effect; the second phase may have its cause in a stimulation of the vagus by the products of decomposed albumins. All patients with liver disease had a reduced alkali reserve. The treatment of these patients by roentgen rays or the administration of a general anesthetic (ether or chloroform) is, therefore, dangerous.

E. A. Pohle.

Pathologic Anatomy

SICKLE-CELL ANEMIA: REPORT OF TWO CASES FROM OHIO ILLUSTRATING ITS HEMOLYTIC NATURE. H. S. ALDEN, Am. J. M. Sc. **173**:168, 1927.

Since Herrick's first case in 1910, 105 cases have been reported in the United States, mostly from Baltimore and the South, all in negroes. It concerns a familial and hereditary disease of both sexes, characterized by peculiar sickle-shaped red cells, anemia, jaundice, underdevelopment, general enlargement of lymph nodes and, in most cases, ulcer of the leg. In one group of cases sickle cells are present in the circulating blood; in another group the red cells assume sickle-shape after being in a closed chamber for some hours; there are gradations of all degrees between these groups. Five necropsies have been reported in which there was found in addition to the anemia with the peculiar forms of red cells, a small, fibrous spleen with old and recent hemorrhages and in some cases marked hyperplasia of the marrow. Alden reports two typical cases from Cincinnati in one of which the ulcers of the legs at first were regarded as syphilitic. In the other case sudden abdominal pain with distention is thought to have been due to a splenic hemorrhage.

XANTHOMA DIABETICORUM: AN UNUSUAL PROCESS OF INVOLUTION. JOHN HARRIS and E. GOLDSTEIN, Am. J. M. Sc. **173**:195, 1927.

A case is described in which the lesions on the palms disappeared completely, and those on the elbows coalesced and left large pigmented patches, while those on the legs and thigh after degeneration resulted in extensive scars. The latter process seems to be undescribed hitherto.

INFARCTS OF THE PLACENTA: A STUDY OF SEVEN HUNDRED CONSECUTIVE PLACENTAS. R. S. SIDDALL and F. W. HARTMAN, Am. J. Obst. & Gynec. **12**:683, 1926.

Four kinds of infarcts are described. The first is a poorly defined, irregular, pearl gray formation, usually in the depths of the placenta, but at times near the surfaces or margins, which microscopically reveals broad projections of fibrin into the surrounding villi, while in the center it is more solid and contains degenerated villi and fragments of nuclei. Such infarcts vary from a few millimeters to several centimeters. The second form is more sharply demarcated, usually rounded or oval, the color varying from shades of red to brown, the lighter colored ones being made up of lamellae of fibrin and coagulated blood. This infarct is usually beside an older infarct, usually of the fourth type, parallel to which the lamellae are laid down. At the periphery, the fibrin is devoid of blood cells and forms a pseudocapsule. The third type of infarct resembles closely the second, just described, except in color, which is a dull white pinkish or brick shade. These three forms of infarcts are due to thrombosis of the maternal blood in the intervillous spaces. The latter are comparable to blood vessels, the villi dipping into the spaces being comparable to the vessel walls, and the syncytial covering acting as an endothelial lining. Such factors as stasis and denudation of the anticoagulative syncytium are the possible causes of infarction. The fourth type of infarct varies from nodules of a few millimeters to an involvement of one or more cotyledons. They are dull white to yellowish, with fuzzy edges sharply contrasted from the normal placenta. They consist of closely packed, equally affected villi with a thin layer of fibrin in between. The syncytial

epithelium may persist longer than the rest of the involved villus. Such infarcts are regarded as a simultaneous involvement of all the branches of a stem villus due to a disturbance of the fetal-placental circulation. The authors found that infarction occurred in 67.7 per cent of the placentas they studied and had no relation to the age and number of pregnancies. All types were found increased in the toxemias of pregnancy; the presence of the infarcts in general did not have any effect on the welfare of the child.

A. J. KOBAK.

STUDIES ON THE ISLANDS OF LANGERHANS IN HUMAN PANCREAS: I. THE RELATION OF THE ISLANDS TO THE SURROUNDING STRUCTURES. SADAO OTANI, Am. J. Path. **3**:1, 1927.

Three types of islands were recognized in the normal pancreas: *A*, islands connected with surrounding acini, found in every case; *B*, islands connected with interlobular and intralobular ducts, and *C*, islands strictly separated from the surrounding structures. The classification of the types was made in the order of their frequency. The islands do not have any fibrous capsule of their own, but a more or less complete separation is produced by the basement membrane of the acini or ducts or by the interlobular connective tissue. There are wide variations in size, shape and relation of the islands to the surrounding pancreatic structures. Such differences are present not only in the same organ but even in the same sections. Therefore, it is improper to speak of one regular type of the island of Langerhans in respect to this relation.

AUTHOR'S SUMMARY.

THE ORGANIZATION OF EXPERIMENTAL ADRENAL CELL EMBOLI IN THE LUNGS. J. P. SIMONDS, Am. J. Path. **3**:13, 1927.

Certain resemblances are pointed out between the histologic tubercle and nodules produced in the lungs of rabbits by the organization of experimental suprarenal cell emboli. This peculiar type of reaction is believed to be due to the high content of lipoid substances, especially cholesterol, contained in the suprarenal cells.

AUTHOR'S SUMMARY.

A QUANTITATIVE STUDY OF THE HYPOPHYSIS OF THE HUMAN ANENCEPHALIC FETUS. W. P. COVELL, Am. J. Path. **3**:17, 1927.

This article is based on the study of thirty-two anencephalic fetuses. An hypophysis, variable in weight, mostly without pars nervosa, with variable pars intermedia, was found to be present.

SYNGENESIOTRANSPLANTATION IN THE GUINEA-PIG AND THE RAT. LEO LOEB, Am. J. Path. **3**:29 and 45, 1927.

In both guinea-pig and rat the syngenesioreactions are intermediate between the reactions in autotransplantation and homoiotransplantation, the reactions being on the whole less in the rat than in the guinea-pig, owing, perhaps, to the greater homogeneity in the genetic composition of the rats used in the experiments. In the guinea-pig race differences between the parents had some influence on the reactions following the exchange of tissue between members of families. Reactions against pieces of different organs from the same donor were relatively of the same strength, although absolutely the reactions might differ because of secondary factors.

PATHOLOGIC CHANGES IN THE NERVES OF THE STOMACH WALL IN CASES OF CHRONIC GASTRIC ULCER. HAROLD OKKELS, Am. J. Path. **3**:75, 1927.

This article is an abstract of a monograph to be published later. It was found that nerves and nerve cells are frequently present in the immediate vicinity of gastric ulcer. Perineuritis is common and may cause pain. From proliferative changes in the nerves neuromas may develop.

TUMOR AND FOREIGN BODY GIANT CELLS IN A FIBROSARCOMA OF THE UTERUS. F. B. MALLORY and FRED W. STEWART, Am. J. Path. **3**:85, 1927.

A fibrosarcoma of the uterus containing tumor and foreign body giant cells in great numbers is reported. The tumor giant cells are formed from multiple mitoses and indicate rapid growth and malignancy. The foreign body giant cells are evidently due to fusion of endothelial leukocytes attracted into the tumor by the intercellular substance left by necrosing tumor cells. The leukocytes are attempting to dissolve the hyaline collagen and have fused for this purpose. Along the surface where they are applied to it a layer of minute rods is formed, which are perhaps altered centrosomes. Osteoclasts present the same structure.

AUTHORS' SUMMARY.

SPONTANEOUS INTRACAPILLARY GLOMERULONEPHRITIS IN THE RABBIT. F. B. MALLORY and FREDERIC PARKER, JR., Am. J. Path. **3**:91, 1927.

Results following experiments on rabbits at first thought to be due to the effect of zinc are now interpreted as probably due to spontaneous glomerulonephritis.

THE PATHOLOGY [PATHOLOGICAL ANATOMY] OF BLACKWATER FEVER. G. H. WHIPPLE, Am. J. Trop. Med. **7**:1, 1927.

Malaria and blackwater fever are much alike in the changes in the organs. There is a circulating poison in both, more intense in blackwater fever.

OBSTETRICAL INJURIES OF THE SPINAL CORD. BRONSON CROTHERS and MARIAN C. PUTNAM, Medicine **6**:41, 1927.

In almost all cases the obstetric injuries of the spinal cord appear to follow traction during delivery. The cases fall, in general, into a few groups. Some show flaccid paraplegia, apparently due to almost complete destruction of the lower cord. "A second group presents lively reflexes dependent upon the isolated part of the transected cord while a third are handicapped by disturbances due to perverted control as a result of partial destruction of afferent or efferent tracts."

DIVERTICULITIS. LIONEL R. FIFIELD, Lancet **1**:277, 1927.

The article is based on 218 examples of acquired diverticula of the large intestine, encountered in 10,167 consecutive postmortem examinations, and in fifty-two clinical cases of diverticulitis.

PARASITIC INFECTION [ACARUS] OF URINARY TRACT. E. C. MEKIE, Edinburgh M. J. **33**:708, 1926.

A case of acarus infection is described involving the pelvis of the right kidney. The symptoms led to a diagnosis of acute appendicitis. Subsequently the mites and their eggs were found in the urine. The acarus in this case was identified as *Tyroglyphus longior*.

THE STRAWBERRY GALLBLADDER: PATHOGENESIS, CLINICAL STUDY AND TREATMENT. M. CHIARAY and I. PAVEL, Ann. d'anat. path. et d'anat. méd.-chir. **3**:669, 1926.

This article represents one chapter from a monograph on the gallbladder to be published by the authors, and concerns itself with the so-called "strawberry gallbladder" only. The term "strawberry gallbladder" was applied by MacCarty to a peculiar lesion of the gallbladder which consists in the presence of small elevated blackish yellow granulations covering the mucosa of this organ and giving to its mucous membrane the appearance of the surface of a strawberry. A similar appearance seems to be due to accumulations of doubly refractive lipoid substances underneath the epithelium. Here, usually at the level of the free extremity of the villosity, one observes groups of roughly round or polyhedral cells measuring from 40 to 50 microns in diameter, and colorable by the ordinary stains. The cytoplasm of the cells is large, and the nucleus containing a fine network of chromatin is eccentric or even pushed to the very periphery of the cells. The meshes of the cytoplasm are infiltrated with lipoids which are revealed by staining with sudan III. The epithelial lining of the mucosa does not show any changes. Besides this peculiar lesion, the wall of the gallbladder shows ordinary inflammatory changes.

The pathogenesis of this lesion is not definitely established. It is probably due to an infectious process leading to a lymphatic stasis while the epithelium continues its normal functions of absorption of lipoids and even cholesterin. Thus, a local cholesterinemia is produced. The endothelial cells lining the lymphatic spaces become infiltrated with fatty substances and with lipoids. During the advance of the process they proliferate and become enlarged, leading to compression of the neighboring tissues and to a dilatation of the villosity at its free end. The clinical diagnosis of the lesion is difficult. Pain is present in the cystic region; jaundice is frequent and is not accompanied by clay colored stools, which is explained on the basis that it is not due to retention of bile but to a biliary infection. The treatment of choice is apparently cholecystectomy.

B. M. FRIED.

ABSCESS OF THE SPLEEN, OF TYPHOID ORIGIN. C. MOREL, C. DAMBRIN and J. TAPIE, Ann. de méd. **19**:5, 1926.

The authors report a case of typhoid fever complicated by an abscess of the spleen, which represented a "large purulent sponge." Typhoidal splenic abscess occurs more often in rather mild cases, sometimes coinciding with the lysis, and sometimes after the temperature has subsided, leading to a relapse. The abscess is usually in the upper pole. In a few instances there were multiple abscesses. Splenotomy is the choice of treatment. The prognosis is favorable. The condition is apparently less rare than it is believed to be.

B. M. FRIED.

ARTERITIS NODOSA, CLINICAL AND ANATOMIC DATA OF A NEW CASE. E. FROMMEL, Ann. de méd. **19**:42, 1926.

The changes of arteritis nodosa consist in the infiltration of the advantitia and of a lymphocytic invasion of the media. There is a proliferation of the intima followed by its detachment from the elastica interna, leading to occlusion of the vascular lumen, to thrombus formation and to infarctions in the neighboring tissues. It is now known that the lesion may exist without producing visible nodules, being recognized, therefore, only on microscopic examination. This and the fact that the lesion may be confined to a few organs only is possibly responsible for the claim that it is a rare disease.

The peripheral nerves, as well as the branches of the vagus, undergo degeneration, as observed by Wohlwill, Schminke and others. The coronary, renal and hepatic arteries are the most frequently affected. Next in order are the vessels of the mesentery, stomach, intestines, spleen, pancreas and muscles. The arteries of the bronchi, of the bladder and of the suprarenals are rarely diseased.

The onset of the disease is insidious, the temperature is not typical and direct somatic symptoms are scant. The patjents usually lose weight and become pale, with a waxy nuance of the skin which is covered with a profuse sweat. The complaints are mostly referred to the digestive, renal and nervous systems. Many patients complain of severe muscular and periarticular pains accompanied by a pitting edema of these structures. In a number of cases the skin showed a scarlet uniform rash, in others it was frankly hemorrhagic, simulating purpura. The cardiac symptoms, in spite of the involvement of the coronary arteries (in 100 per cent of cases according to Mönkeberg), are insignificant. Tachycardia is present, but the blood pressure is normal. The blood shows a leukocytosis and a marked secondary anemia.

B. M. FRIED.

AN ATYPICAL FORM OF "PROGRESSIVE HYPERTROPHIC NEURITIS." A. SOUQUES, Ann. de méd. **19**:484, 1926.

According to the symptoms, the disease can be differentiated into two types: 1. The type Gombault-Déjerine is characterized by a muscular atrophy of all four extremities. The atrophy in such cases is more pronounced at the extremity than at the root of the limb; it begins with the legs, where it is usually more accentuated and is accompanied by fibrillary twitchings and disturbances in electric reaction. There are present tabetic signs, lightning pains, anesthesia, Romberg's phenomenon, the sign of Argyll-Robertson, myosis, motor incoordination and abolition of the tendon reflexes. Nystagmus and a marked kyphoscoliosis are also present. 2. The type of Pierre-Marie-Bovery is characterized by a muscular atrophy of all four extremities, in which fibrillary twitchings, tabetic pains, motor incoordination, a Romberg sign and an Argyll-Robertson sign are lacking. Myosis or nystagmus are not seen. The tendon reflexes are, however, abolished; there is a marked kyphoscoliosis and also signs typical of sclerosis en plaques such as intentional tremor and scanning speech.

In both of these varieties the essential is the increase in size of the peripheral nerves. This is the primary and constant symptom which controls, so to speak, the amyotrophy and the areflexia. All the other symptoms are secondary and inconstant. All peripheral nerves, superficial and deep, with the exception of the optic and acoustic, are involved. Macroscopically, they have doubled in size. The roots of the nerves have the same aspect; the lesion here, however, is more recent and less marked. Microscopically the epinerves and endonerves are only slightly thickened. The nerve fibers and the peritubular connective tissue are severely damaged; the axis cylinder is often preserved; the sheath of Schwann is enormously hypertrophied, surrounding the axis cylinder in several layers overlapping each other. The latter makes up the principal lesion, and the neuritis appears primarily as a "Schwannitis." The muscular atrophy is secondary. Although neuritis means involvement of the peripheral nerves only, the cases are frequently accompanied by alterations in the spinal cord, which, however, are slight and like the muscular atrophy, are secondary to the involvement of the peripheral nerves.

The disease, the first as well as the second, is familial; it begins in infancy and progresses gradually. The etiology of the disease is unknown. It occurs certainly more frequently than is believed. Souques reports in detail a case of this interesting disease observed by him.

B. M. FRIED.

THE IMPORTANCE OF ARTERIAL LESIONS IN THE PATHOGENESIS OF RAYNAUD'S SYNDROME. H. GRENET and ISAAC-GEORGES, Ann. de méd. **20**:27, 1926.

Two theories are advanced to explain Raynaud's disease: (1) the nervous theory; (2) the vascular theory. The nervous theory regards the phenomenon as a functional disturbance of sympathetic origin. The vascular theory considers the vascular lesion as being the primary pathogenic factor in the disease, while the involvement of the sympathetic system gives to the disease its paroxysmal character.

The nervous theory is favored by the fact that the disease is paroxysmal, occurring frequently in young women without any history of accidents predisposing to arterial lesions. Then again, in the interval between attacks, the circulation in the affected organs is normal. This theory, however, is powerless to explain the symmetrical localization of the accidents, and also the curious typography of the lesion, that is to say, the involvement of only one finger of each hand or one toe of each foot. The latter can be easily explained by the fact that the vessels of this particular area are involved.

Grenet and Isaac-Georges report their experience with a few cases which they have investigated clinically and anatomically. They believe that two factors lead to Raynaud's syndrome: (1) lesions in the arteries which are apparently present not only in the terminal vessels of the extremities, but also in the larger vessels; (2) a disequilibrium of the vegetative nervous system often connected with endocrinian disturbances predisposing to the spasmodic phenomenon characteristic of the lesion.

B. M. FRIED.

THE AORTA IN PALUDISM. E. BENHAMOU, Ann. de méd. **20**:145, 1926.

Certain French clinicians believe that there exists an aortitis of malarial origin. Benhamou investigated the aorta of a number of patients with malaria by the use of roentgen rays. His study indicates that there is no aortitis in such patients, but a functional dilatation of the ascending part of the arch of the aorta. The lesion is accompanied by retrosternal pain and dyspnea, which is not difficult to differentiate from angina pectoris. Quinine is, of course, the treatment of choice.

B M. FRIED.

A NEW INDUSTRIAL DISEASE DUE TO MANIPULATION WITH RADIOACTIVE SUBSTANCES: NECROSIS OF THE JAW. A. LACASSAGNE, Paris méd. **16**:132, 1926.

Lacassagne emphasizes the need of a law for protection of workers exposed to radioactive substances. His plea is founded mainly on the reports of the American authors Hofmann and Martland, Coulon and Knef (*J. A. M. A.* **85**:1769 [Dec. 5] 1925) on necrosis of the jaw in workers who paint radioactive material on watch dials. Lacassagne produced similar lesions in rabbits by injection of polonium. The disease is not observed among the watch makers of Switzerland and France who use rods for putting the illuminating substance on the dials.

W. HUEPER.

THE LYMPHATIC ORGANS. L. ASCHOFF, Beihefte z. med. Klin. **22**:1926.

After disussing the general structure of lymphatic tissue, Aschoff states that the functions of the germinative centers in lymph nodes are production of lymphocytes and neutralization of toxic substances. The regeneration of lymphoblasts takes place probably either from old ones or from reticulum cells.

The lymphocytes do not possess phagocytic or lipolytic power or special affinity for substances as proteins or carbohydrates. Their function is probably a fermentative one, because they are found in the blood and the chyle and are increased after digestion. The tonsils are not regarded as organs for special protective purposes or as receptacles for pathogenic bacteria. Their frequent infections are due to peculiarities in location and structure. The lymphatic tissue of a new-born is poorly developed, but grows rapidly, reaching its climax at the tenth year. The frequent infections during this period are regarded as one of the causes of this course. A second climax may be seen in old age. The plasma cells so often present in large number in lymphoid tissue are regarded as changed lymphocytes and not as the mother cells of the lymphocytes. Whether eosinophilic myelocytes originate from adventitial cells of the capillaries of lymphoid tissue remains undecided. Reticulum cells and reticulo-endothelial cells are closely related. The reticulo-endothelial cells store small particles as dyes, coal dust and lipoids more readily than the reticulum cells. As the lymph circulates in the sinuses and lymphatics, foreign bodies and toxins are removed from the lymph nodes. There is a relation between nutrition and the amount of lymphatic tissue. It is well developed in well fed persons, and hypoplastic in the undernourished. The genuine status lymphaticus is regarded as due to congenital disposition caused by endocrine disturbances. A secondary metabolic status lymphaticus may be produced by exclusive and excessive feeding with certain proteins, and a secondary status results also from chronic infections of mucous membranes. Status lymphaticus is interpreted as a symptom of an unusual irritability of the organism of an unknown character. The causes of a localized lymphatic hyperplasia are acute or chronic infections, producing a regenerative hyperplasia of the germinative centers and an increase of the lymphoid tissue, which is transformed into a myelic tissue in pernicious anemia and myelogenous leukemia. Alterations of the reticulum cells and reticulo-endothelial cells are produced by changes of the lymph. After injections of vital stains, swelling and proliferation of the reticulo-endothelial cells and liquefaction of the reticulum is observed. The reticulo-endothelial cells of the perifollicular sinus take up living particles like tubercle bacilli more readily than dead substances. Their subsequent necrosis instigates a regenerative proliferation. A fibrosis of the lymph nodes is the result of an atrophy of the lymphatic tissue with collapse of the reticular network. Sclerosis follows infectious processes and induration is produced by the deposition of dead particles, such as dust, with secondary proliferation of connective tissue and transformation of the reticular fibrils into collagenous fibrils. Hyalinization is caused by a transformation of tuberculous epitheloid cell proliferations into scar tissue with deposition of hyaline material into the interfibrillar spaces. The predilection of the peripheral zone for the deposition of amyloid is of unknown nature. The relation of the lymphatic organs to the endocrine system are demonstrated by the hyperplasia of the lymphatic and lymphoid tissue in exophthalmic goiter. The mesenteric lymph glands are important for the lipoid metabolism, because the reticulo-endothelial cells transform the lipoid into neutral fats. The reticulo-endothleial cells are also regarded as producers of antibodies. Lymphocytosis may be caused by hyperplasia of the lymphatic tissue, as in childhood; lymphopenia is due either to destruction of lymphatic tissue (tuberculosis, typhoid fever) or to a functional inability of the lymph glands to release lymphocytes into the lymph and the blood. The transformation of lymphatic tissue into lymphoid or reticulo-endothelial tissue, and vice versa, may occur under pathologic conditions.

W. HUEPER.

RESEARCHES ON THE PHYSIOLOGY OF THE WHITE CELLS: CYTODIAGNOSIS AND ITS CLINICAL APPLICATION. A. ALEXEIEFF, Centralbl. f. Bakteriol. **101**:240, 1926.

This paper, illustrated with plates and figures, deals with the morphology and function of the various white corpuscles. The plasma cells are considered to have as their principal function the absorption of poisonous substances: first, because of the basophilic tendency of the cytoplasm, and second, because of the evidences of degeneration as shown by the peripheral pyknosis of the nucleus and the hyaline bodies of Russel in the cytoplasm, these giving evidence of a cell profoundly intoxicated. The author points out, however, that a small proportion are phagocytic and he calls these plasmophages.

The monophages, however, have the power of phagocytosis to a marked degree of erythrocytes, other white corpuscles, bacteria, etc.

The lymphocytes are claimed to produce a lipase, but mainly are conceived to be "toxinophagic," electively absorbing toxic substances. The neutrophilic leukocytes, besides their phagocytic function, have mainly the ability to elaborate proteolytic enzymes and to produce glycolytic enzymes for the general reaction of glycogenolysis.

The author then discusses the theory of "second degree digestion," which maintains that in general digestion and assimilation the white cells play an important rôle, not only in carbohydrate, but also in nitrogenous and fat metabolism. Furthermore, phagocytosis and the entire problem of immunity is only a particular case of this doctrine of "second degree digestion." The great importance of the mesenchymal tissues as a whole is particularly stressed, emphasizing the functional properties of phagocytosis, detoxication and ferment action possessed by the various calls of this tissue which Alexeieff calls, in general, the phagonephro-endocrinocytes.

PAUL R. CANNON.

PANCREAS CELL-ISLANDS AND INSULIN AFTER LIGATION OF THE PANCREATIC DUCTS. G. HERXHEIMER, Klin. Wchnschr. **5**:2299, 1926.

Ligation of the pancreatic ducts of chickens caused atrophy of the parenchyma of the pancreas, huge increase in the cell islands and an increase of the insulin content of the pancreas up to five times the normal.

J. D. WILLEMS.

ESSENTIAL HYPERCHOLESTERINEMIA WITH XANTHOMATOSIS OF THE SKIN AND FAMILIAL CHOLELITHIASIS. A. PANZEL, München. med. Wchnschr. **73**:2119, 1926.

In a woman, aged 31, cholelithiasis and xanthomatosis of the skin had been present since puberty. The cholesterin content of the blood serum was 0.812 per cent; that of the bile 0.4 per cent; and that of the gallstones 96 per cent.

J. D. WILLEMS.

SUPRARENAL TUBERCULOSIS WITH PERFORATION INTO THE STOMACH. M. NORDMANN, München. med. Wchnschr. **73**:2123, 1926.

The postmortem examination of a man with the clinical symptoms of Addison's disease and peptic ulcer demonstrated bilateral caseous tuberculosis of the suprarenal glands, with direct extension and perforation from the left into the lesser curvature of the stomach.

J. D. WILLEMS.

A Case of Anonychia Congenita with Assimilation of the Phalanges. A. Dombrowski, München. med. Wchnschr. **73**:2168, 1926.

Nine toe nails and the distal phalanges of all except the two great toes are congenitally absent in a male adult patient described. J. D. Willems.

Effect of Roentgen Rays and Radium on the Mandible. M. Leist, Strahlentherapie **24**:268, 1926.

The observation of several cases of injury following irradiation of the region of the mouth, teeth and mandible, induced the author to study experimentally the effect of roentgen rays and radium on teeth and mandible in rats and dogs. It appears that the rays injure the odontoblasts chiefly in the germ zone. Changes in the cement were not seen. The growth of teeth in young dogs may be stopped by irradiation, the teeth may even fall out; the periodontium, alveolar process and bone marrow show pathologic changes. Following from two to five erythema doses the mature molars of rats show atrophy of the pulp. Studies were made on patients who received treatment over the mouth region and on young children whose mothers had been irradiated over the pelvis during pregnancy. In the first group, the electrical reaction of the teeth was still positive, while definite injury could be demonstrated by other methods. This is explained by a low sensitivity of the nerve tissue to radiation; in the second group, the dentition appeared to be delayed. E. A. Pohle.

Osteodystrophia Fibrosa [Osteitis Fibrosa]. E. Christeller, Verhandl. d. deutsch. path. Gesellsch. **21**:7, 1926.

In autopsies on patients with bone diseases the skeleton as a whole, habitus, proportions and single bones, should be studied; photographs and roentgenograms should be made of the skeleton or the most important bones; the whole skeleton, or at least the skull, ribs, vertebrae, pelvis and a few long bones should be examined carefully; material for maceration and moist conservation should be selected; the glands of internal secretion and organs with metastatic calcifications should receive special attention. Changes typical of osteitis fibrosa are the extensive resorption and simultaneous excessive new formation of bone tissue and the transformation of the bone marrow into fibrous tissue, while in the malacic diseases the insufficient calcification of osteoid tissue is the main change, and fibrosis of the marrow is found only after trauma. Osteitis fibrosa starts with an increase in the activity of the osteoblasts. This process is followed by a proliferation of the bone marrow and apposition of new bone by the endosteum. If these processes are well balanced change does not occur in the macroscopic appearance of the bone. A predominance of the osteoclastic activity will result in a rarefaction of the bony substance, while an osteoblastic increase will produce a thickening. The newly formed bone in early and progressive cases is porous, but changes later, especially in cases with a slow course, into a bone of an ivory-like character, representing the end-result of the disease. Deformities of the bones are most frequently found in the porotic type (kyphoscoliosis, elongation, thickening and curvatures of the long bones, elevation of the base of the skull, etc.). Fractures are often numerous. All these deformities are fixed by the subsequent sclerosis. Another factor of influence on the symptoms of the disease is the age of the patient. Osteitis fibrosa in childhood causes disturbances of the epiphyseal growth resulting in thickening of the joint regions, production of rosary, defects in the calcification zone, etc.

On account of these pseudorachitic symptoms, an infantile type is distinguished from the common adult type and the sclerotic senile type. Osteitis deformans, or Paget's disease, ranks in this classification as an adult hyperostotic-porotic type and is not regarded as a disease *sui generis*. The giant cell sarcoma of bone in osteitis fibrosa is interpreted as a benign, cellular proliferation with resorptive functions and is not specific, being also found in Koehler's disease (tarsal scaphoiditis), hematoma of bone, pseudarthrosis, delayed fracture and other conditions. The benign character is shown by multiplicity, circumscribed growth, which is arrested at the periosteum, location at places on which a special strain is exerted, the regularity and maturity of cells and the cluster-like arrangement of the giant cells. Metastases from these tumors as such are never observed. The solitary myelogenous giant cell sarcomas and epulides are considered as belonging to this group of tumors and representing probably a special type of localized osteitis fibrosa. Hyperostotic formations appear often symmetrically in the tibia or on the skull, where they produce a picture known as "leontiasis ossea." Similar changes may be due to rickets, syphilis, metastatic carcinosis of the bone and primary bone tumors. Leontiasis ossea is therefore only a symptom and not a disease. Osteitis fibrosa is a disease that affects in general the whole system. Reports of localized forms are mostly due to incomplete examination of the skeleton. The clavicles and the long bones are especially involved in this type. The development of malignant tumors from giant cell sarcomas is reported in several cases and the giant cell sarcomas are regarded as presarcomatous formations. The cystic formations in the bone, regarded as due to liquefaction of the tissue of the giant cell tumors, represent their final stage; according to some, they may result from small hemorrhages into the marrow which continue and progress for some time due to the hydrostatic pressure and venous congestion, ending in a cyst. Differentiation from syphilis of the bone rests on the porous character of the bone, the wide marrow cavity and the normal periosteum in osteitis fibrosa, and the ivory-like bone, the narrow marrow cavity, the periosteal osteophytes in syphilis. The classification of "fragilitas ossium" (Albers-Schönberg) is difficult and has to remain undecided. Rickets and osteomalacia do not represent a basis for a secondary osteitis fibrosa. But mixed forms were observed. Changes in bone from starvation show alterations which are sometimes similar to those seen in hypostotic-porotic osteitis fibrosa, while others resemble more those of osteomalacia. Moeller-Barlow's disease, trophic osteoporosis and senile osteoporosis differ from osteitis fibrosa by their lack of increased resorption of bone substance. The osteoporosis in Recklinghausen's disease cannot be classified. Observations on disturbances in the calcium metabolism are insufficient to allow definite conclusions. In cystic osteitis fibrosa a retention of calcium was observed. A diet deficient in calcium in a case of hyperostotic-porotic osteitis fibrosa produced a higher blood calcium level and a negative calcium metabolism; the condition changed after a diet rich in calcium only by increasing the blood calcium. The hypostotic type in monkeys has an increased calcium elimination, while the hyperostotic type shows a calcium retention. Hyperplastic proliferations of the parathyroid glands are frequent in osteitis fibrosa, but their significance is doubtful and may be compensatory. Osteitis fibrosa has been observed also in animals (swine, gazelles, goat, opossum, cattle, horse, dog, porcupine and monkey). The horses have mostly a condition of the jaw representing a hyperostotic-porotic type. The old world monkeys show only the hyperostotic type, while the new world monkeys show exclusively a hypostotic type. The gundu of the African monkeys is an osteitis fibrosa of the nose.

W. HUEPER.

THE CLINICAL ASPECTS OF OSTEODYSTROPHY FIBROSA [OSTEITIS FIBROSA]. P. FRANGENHEIM, Verhandl. d. deutsch. path. Gesellsch. **21**:49, 1926.

Frangenheim recognizes, besides the juvenile, adult and senile types mentioned by Christeller, a congenital form. This is the cause of intra-uterine fractures of the tibia (congenital pseudarthrosis). Its prognosis is unfavorable. Early radical operation in a few cases was successful; usually amputation of the leg is necessary. A disturbance of the embryonic anlage of the bone is regarded as a more important etiologic factor than trauma. Of the juvenile and adult types, circumscribed osteitis fibrosa of the skull starts in early childhood and produces the first pronounced symptoms in the second or third decennium; the temporal region is mostly affected; there is progressive headache, paresis of brain nerves and exophthalmus, and the roentgen-ray examination shows thickening of the bone with indistinct outlines and unequal density of the shadows in places; after resection of bone and secondary autotransplantation, recurrences are rare. Leontiasis ossea involves mainly the facial part of the skull and results from progressive mild infection from sinuses (Knagg), ending in osteitis fibrosa. Gundu starts as a juvenile hyperostotic-porotic type which changes later into an adult hyperostotic-sclerotic type. Genralized osteitis fibrosa occurs especially in females in the fifth and sixth decenniums. Infectious diseases and nutritive, metabolic and endocrine disturbances play a part in the causation. Parathyroid enlargements are often but not regularly present. The blood shows secondary anemia due to fibrosis of the marrow. The course either ends in death after a few years, with marked malacia of the bones, or continues over many years. Pregnancy should be avoided. Resection, with autotransplantation and crushing of the cysts to remove the tension and to relieve the patient from pains, may be attempted. Oöphorectomy is without success, also transplantation of parathyroid glands. After removal of parathyroid glands improvement has been observed. Roentgen-ray treatment arrests the osteoclastic processes and produces fibrosis. Circumscribed solitary cysts are frequent and may be found in almost every bone, especially in the shafts of young persons. The epiphyses are rarely involved. The wall is thin and friable, and the cavity filled with serous or serohemmorrhagic fluid. There may be one or more compartments and no cellular lining. The cause may be trauma with damage to the endarteries of the epiphyseal line, followed by necrosis of the corresponding bone, and resorption by osteoclasts, infectious diseases (scarlatina, appendicitis, angina), congenital syphilis (perhaps indirectly through its effect on the endocrine system), rickets, osteomalacia, malnutrition, circulatory and blood disturbances, anemia, local disposition and other conditions. After spontaneous or surgical fracture of the cyst or curettement of the cystic wall, the cavity is filled by a sclerotic fibrous tissue which is later transformed into bone tissue. Of the senile type (Paget's disease, osteitis deformans), more than 350 cases have been reported. It may occur in families. Sclerosis of the spinal cord and intestinal intoxication by acid producing bacteria are considered as causative factors besides those mentioned. A lymphocytosis and monocytosis, retention of calcium, magnesium and phosphorus and decrease of the sulphur of the blood are observed. Many bones are affected, especially long bones of the lower extremities, clavicle and skull. Neuralgic or rheumatic pains are felt in the affected parts and increased temperature and redness of the skin over the diseased areas. The course is slow without interference with the general health. The disease starts usually after forty and may last many years. The attitude of the patients resembles that of the anthropoid apes (the spine is kyphotic, the arms hang low down, the head is stretched forward, the chin is raised, the

face is thin and the legs are bent in the knees). The skull is enlarged and the forehead appears to be high on account of baldness. The occipital foramen is narrowed. The disease appears to be rare in this country, while the localized type, involving usually the tibia, is frequent in Germany. The administration of ovarian preparations and removal of sexual glands has not had any effect. Improvements were seen in some patients treated with compounds of arsenic, mercury, iodine, calcuim and phosphorus; also after epinephrine, thyroid substance, tuberculin and quinine. Removal of the parathyroid glands and roentgen-ray radiation were successfully tried. Surgical operations are contraindicated on account of frequent subsequent pseudathroses. W. HUEPER.

OSTEITIS FIBROSA. G. SCHMORL, Verhandl. d. deutsch. path. Gesellsch. **21**:71, 1926.

Schmorl found twenty-five cases of osteitis fibrosa among 32,000 autopsies before October, 1925. Since then he saw eighteen more cases among 650 autopsies (2.75 per cent against 0.062 per cent in the previous period) after starting routine examination of the skeleton. The macroscopic diagnosis was possible after some experience, but microscopic examination was made in all cases. Skull, sternum, ribs, femur, vertebrae, pelvis and diseased bones were regularly examined. The vertebrae were most frequently involved, showing porous densities underneath the vertebral disks; in the other bones those alterations were usually present in the subchondral regions. In the differential diagnosis, the presence of a mosaic structure of the newly formed trabecula in osteitis fibrosa is emphasized. This mosaic structure is due to resorptive and appositive processes in small areas of the bone and is especially seen in the hyperostotic type, but never in any other disease of the bones accompanied by regenerative processes (callus, rickets, osteomalacia, bone tumors, hyperostoses, syphilis and fragilitas). The progressive atrophy of bone is regarded as a special type of osteitis fibrosa on account of the giant cell sarcomas observed, the excessive resorptive and appositive processes and tumors of the parathyroid glands. Hunger osteopathy is sometimes similar in structure to osteitis fibrosa but is interpreted as an osteomalacic process. Degeneration of articular cartilage and cartilagenous proliferations on synchondroses were observed in osteitis fibrosa. Cases were seen with remissions or spontaneously healed foci in some of the bones and active processes in others. W. HUEPER.

THE DEVELOPMENT OF OSTEOCLASTIC RESORPTION TISSUE AND GIANT CELL EPULIS. H. SIEGMUND, Verhandl. d. deutsch. path. Gesellsch. **21**:86, 1926.

After implantation of fresh, boiled or autolyzed pieces of bone into the subcutaneous tissue of animals the development of a mesenchymatous tissue containing many giant cells and showing a specific resorptive function was observed (formalinized bone did not produce such a reaction). The resorption of the bone was caused by osteolysis and osteoclasts which were partly derived from osteocytes. The osteoclastic tissue resembled the giant cell sarcomas present in fibrous osteitis and is interpreted as the reaction to the presence of dystrophic bone. The giant cells are derived from cells of the local connective tissue from those of the wall of the vessels and perhaps also from osteocytes. The alterations in fibrous osteitis are possibly not caused by a specific factor. The giant cell epulis belongs to the giant cell tumors of bone and is caused by dystrophy in the alveolar process. Osteofibroma of the jaw represents its end-result.

W. HUEPER.

PATHOGENESIS OF OSTEITIS FIBROSA OF VON RECKLINGHAUSEN. E. LOOSER, Verhandl. d. deustch. path. Gesellsch. **21**:91, 1926.

Osteitis fibrosa is not etiologically a specific disease, but it includes different diseases producing similar anatomic lesions of the bone. Ostetis deformans is interpreted as the result of a chronic inflammatory disease of the bones of unknown etiology. Bone cysts and giant cell tumors are the result of the reactive processes following hemorrhage into bone. They are always localized processes and do not have any relation to the generalized osteitis. Localized chronic irritations may also produce a solitary granulation tissue containing giant cells, but it is also found in generalized bone diseases (osteitis deformans, rickets, osteomalacia, osteoporosis).

W. HUEPER.

A CASE OF OSTEITIS FIBROSA WITH MULTIPLE TUMORS IN THE ADJACENT MUSCLE TISSUE. FOLKE HENSCHEN, Verhandl. d. deutsch. path. Gesellsch. **21**:93, 1926.

A case of osteitis fibrosa of the femur with multiple myxomatous tumors in the adjacent muscles of the thigh is reported. These tumors were interpreted as regionary metastases of the fibrous tissue in the bone, which showed the typical structure of fibrotic marrow in osteitis fibrosa.

W. HUEPER.

TWO CASES OF OSTEITIS FIBROSA OF VON RECKLINGHAUSEN WITH TUMORS OF THE PARATHYROID GLANDS. R. PENECKE, Verhandl. d. deutsch. path. Gesellsch. **21**:97, 1926.

Two patients with osteitis fibrosa died at an early stage of the disease from intercurrent diseases. The lack of osteoid tissue around the newly formed bone trabecles was remarkable. In both cases enlargement of one of the parathyroid glands were seen and interpreted as functional hyperplasias. The tumor of one of the cases was composed mainly of eosinophilic cells which were also increased in the blood, hypophysis and bone marrow. Extensive metastatic calcifications in various organs were present in this case.

W. HUEPER.

A CASE OF PAGET'S DISEASE. R. HANSER, Verhandl. d. deutsch. path. Gesellsch. **21**:103, 1926.

The clinical symptoms and the course of a case of osteitis deformans that developed after a sunstroke in 1903 are described in detail. The disease was assumed to be due to alterations of the hypophysis and epiphysis produced by the sunstroke.

W. HUEPER.

ON THE PHAGOCYTIC CAPACITY OF THE BLOOD VESSEL ENDOTHELIUM OF THE FROG'S TONGUE AND ITS PRESUMED TRANSFORMATION INTO WANDERING CELLS. FRANCES STILWELL, Folia haemat. **33**:81, 1926.

The potentialities of the endothelium lining the blood capillaries have produced a great deal of discussion. By some investigators the endothelium is considered to be endowed with characteristics proper to embryonic connective tissue, i. e., to store vital dyes, to be phagocytic par excellence and, finally, to transform itself under pathologic conditions into free macrophages (endothelial leukocytes or endothelial phagocytes). By others the endothelium of the blood vessels is considered capable only of forming new capillaries or becoming transformed into fibroblasts. This "simple" endothelium, according to these writers, ought to be differentiated from the "specific" endothelium which lines the blood

sinuses of the spleen and also of the liver (the Kupffer cells). The latter cells belong to the macrophage system and display all the characteristics proper to this particular group of cells.

Among recent investigations the work of Georg Herzog is of interest in that it shows that the "simple" endothelium of the frog stores vital dyes and also that under such a stimulus it produces wandering cells (macrophages). According to Herzog then, the specificity of the endothelium of the common blood vessels is no longer tenable.

The purpose of Stilwell's study was to test Herzog's statement. Her conclusions are that the endothelium of the vessls of the frog's tongue is able to store particulate matter temporarily, but its ability to be transformed into free ameboid cells could not be traced. The fine technic used in the experiments is given in detail. The article is accompanied by eight figures.

B. M. Fried.

The Hemopoietic Potency of the Small Lymphocyte. William Bloom, Folia haemat. **33**:122, 1926.

Is the small lymphocyte an "end product" in the hematopoietic ladder or can it be transformed into other cells? Schridde, Naegeli, Ferrata, Bunting and Muston believe that the small lymphocyte is a mature element. Pappenheim, Downey and Weidenreich, Kigono and particularly the French and Russian hematologists, ascribe to the small lymphocyte qualities of an undifferentiated embryonic cell. Maximow, for instance, affirms that under certain conditions, as in inflammation, it may hypertrophy and transform itself, after migration into the tissues, into macrophages or polyblasts. The epithelioid cells forming the tubercle in tuberculosis originate, according to this author, from the local histocytes and also from the small round cells. The small lymphocyte may transform itself into a large lymphocyte or lymphoblast of the myeloid tissue. Moreover, it is regarded as a resting hemocytoblast, which under certain stimuli may hypertrophy and give rise to myelocytes, erythroblasts and megakaryocytes.

Bloom has investigated the spleen and the lymph nodes of guinea-pigs sensitized to chicken erythrocytes. He found in the germinal centers of lymph follicles of those organs typical small pseudo-eosinophilic myelocytes, and he believed that they have arisen in situ by the differentiation of special granules in the cytoplasm of small and medium sized lymphocytes.

B. M. Fried.

Pathologic Chemistry

Blood Serum Calcium in Leprosy. I. I. Lemann, R. T. Liles and F. A. Johansen, Am. J. Trop. Med. **7**:61, 1927.

Blood serum calcium is normal in lepers. Relationship does not exist between the calcium content of the blood and bone absorption in lepers. The blood calcium level has not been found to be affected by leprous fever or by other temporary changes in the status of the patient. Administration of chaulmoogra oil does not affect the level of the blood calcium.

Authors' Summary.

Blood Sulphur in Normal and Morbid Conditions. M. Loeper, Progrès méd. **53**:1701, 1926.

Blood sulphur is derived partly from food, partly from tissue disintegration and lysis of red corpuscles. The amount of sulphur in healthy adults is from 0.07 to 0.1 Gm. per liter of blood serum; 80 per cent is represented by

oxidized sulphur, 20 per cent by neutral sulphur. The balance is maintained by a double mechanism. On one side, the sulphur is used by the tissues in the formation of albumin and pigment. On the other side, it is eliminated by the hair, skin, lungs and especially the bile and kidneys. Fasting, intake of water and tissue hydration, as in edema, reduce the content of sulphur in the blood. Ingestion of meat, thirst and pregnancy increase it. An increase may be observed in certain pleuropulmonary diseases, cancer, purpura and even polycythemia. In chronic nephritis, the sulphur parallels the nitrogen. However, in the physiologic and pathologic conditions mentioned, the proportion of oxidized sulphur remains unchanged. Reduction in oxidized sulphur occurs only in diseases involving the liver or the suprarenals. A large part of sulphur is retained in the liver; it is there oxidized and transformed into conjugate sulphates and is eliminated with the bile under the form of taurine. It is the neutral sulphur almost exclusively that is retained by the suprarenals. Accumulation of sulphur in the organism is frequently associated with that of amines; thus, melanin is formed. Pigmentation in hepatic and especially in suprarenal insufficiency is the result of an excess of nonoxidized sulphur in the blood.

THE ALKALI RESERVE OF THE BLOOD IN THYROID DISEASES. E. HERZFELD, München. med. Wchnschr. **73**:2153, 1926.

A normal alkali reserve was found in the blood of a cretin and a marked reduction of it in twelve patients with hyperthyroidism. J. D. WILLEMS.

BLOOD PROTEINS IN SURGERY. H. ACHELIS, Zentralbl. f. Chir. **53**:2774, 1926.

In severe acute inflammatory processes, the Rohrer-Adler and Leendertz methods showed an increase in the globulin. As improvement took place there was a return toward the normal albumin and globulin relations. In marked disturbances of blood protein ratios, surgical operations and general anesthesia should be conducted with special care.

Microbiology and Parasitology

THE TROPICAL SPLENOMEGALY OF STRONG AND SHATTUCK, MARK F. BOYD, Am. J. Trop. Med. **7**:21, 1927.

Strong and Shattuck advanced the view that in the Amazon basin there occurs a splenomegaly that is not malarial in origin, but Boyd holds that it is due to malarial infection.

KALA-AZAR. ROGER BROOKE, Am. J. Trop. Med. **7**:27, 1927.

The patient [Ancon Hospital] presented most of the symptoms and findings encountered in kala-azar. The diagnosis was corroborated by the finding of the parasites in the material obtained by splenic puncture.

AUTHOR'S SUMMARY.

THE VALUE OF CULTURAL METHODS IN SURVEYS FOR PARASITIC AMEBAE OF MAN. CHARLES F. CRAIG and J. H. ST. JOHN, Am. J. Trop. Med. **7**:39, 1927.

In a survey with cultural methods thirty-nine of seventy-one persons were found to harbor amebae, that is 54.92 per cent. *Endamoeba histolytica* was present in eleven, or 15.49 per cent. The Locke serum medium gave a larger

percentage of positive results than any of the larger mediums used. It has been found that *Endamoeba histolytica* can be grown readily in a medium of seven parts of physiologic sodium chloride solution and one part of inactivated human blood serum.

PULMONARY ACARIASIS IN MONKEYS. D. M. GAY and ARNOLD BRANCH, Am. J. Trop. Med. **7**:49, 1927.

Twenty cases of pulmonary acariasis are reported in twenty-five monkeys dying with enterocolitis or tuberculosis. The mites were found encapsulated in small subpleural vesicles, causing a chronic benign infection. The lesions may be distinguished grossly from tubercles by being impalpable, level with the lung surface or slightly umbilicated, unassociated with pleural reaction and yellowish gray without a milky translucent area. AUTHORS' SUMMARY.

UNDULANT FEVER AS A PUBLIC HEALTH PROBLEM. THOMAS G. HULL and LUTHER A. BLACK, J. A. M. A. **88**:463, 1927.

Four cases from Illinois are reported that may have been transmitted by cattle or hogs. Of sixty-nine blood samples that did not agglutinate the typhoid bacillus, five agglutinated *Brucella abortus* in dilutions of 1:200 or higher.

LYMPHATIC UVEITIS CAUSED BY THE VIRUS OF HERPES SIMPLEX. L. R. GIFFORD and L. H. LUCIE, J. A. M. A. **88**:465, 1927.

The results of experiments on rabbits appear to lend support to the view that a filtrable virus may be the cause of sympathetic ophthalmia.

FURTHER OBSERVATIONS ON THE TOXINS OF HEMOLYTIC STREPTOCOCCI. MARY B. KIRKBRIDE and MARY W. WHEELER, J. Immunol. **13**:19, 1927.

Although as a result of further studies it may be possible to distinguish a specific group of scarlet fever streptococci, up to the present, in toxin neutralization tests with a serum produced with the Dochez scarlet fever strain, fundamental differences have not been found in the strains isolated from typical cases of scarlet fever and in those isolated from many other infections.

AN EPIDEMIOLOGICAL STUDY OF ENDEMIC TYPHUS (BRILL'S DISEASE) IN THE SOUTHEASTERN UNITED STATES: WITH SPECIAL REFERENCE TO ITS MODE OF TRANSMISSION. KENNETH F. MAXCY, Pub. Health. Rep. **41**:2967, 1926.

A disease giving a positive Weil-Felix reaction, and clinically indistinguishable from typhus fever except with regard to its relative mildness and low fatality rate, is endemic in the southeastern United States. The epidemiology of this disease appears to differ significantly from that of Old World typhus. The epidemiologic characteristics do not afford any evidence suggesting louse transmission and are interpreted as being at variance with man-to-man transfer by lice, unless it is assumed at the same time that the disease occurs mostly in unrecognizable form. It is suggested as an hypothesis which seems to afford a more probable explanation of the mode of transmission that a reservoir exists other than in man, and that this reservoir is in rodents, probably rats or mice, from which the disease is occasionally transmitted to man.

AUTHOR'S SUMMARY.

CULTIVATION OF VIRULENT BACTERIA FROM ENCEPHALITIC VIRUS. ALICE C. EVANS, Pub. Health Rep. **42**:171, 1927.

Six strains of so-called virus were studied bacteriologically. Four of the strains were originally from vesicles in cases of herpes, one was from the cerebrospinal fluid in a case of syphilis and one was from the brain in a case of epidemic encephalitis. Cultures of virulent streptococci, and cultures of a spore producing rod were obtained from all six strains.

AUTHOR'S SUMMARY.

ACUTE RHEUMATIC FEVER. F. BEZANÇON and MATHIEU-PIERRE WEIL, Ann. de méd. **19**:81, 92, 117, 175, 184, 202 and 225, 1926.

The six articles represent a critical summary of the present knowledge of acute articular rheumatism. The presentation is comprehensive and scholarly, and is illustrated by numerous clinicopathologic observations.

B. M. FRIED.

VIRULENT FILTRABLE ELEMENTS OF THE TUBERCLE BACILLUS. A. CALMETTE and J. VALTIS, Ann. de méd. **19**:553, 1926.

Fontes, of the Oswaldo Cruz Institute at Rio de Janeiro, by investigating, in 1910, the so-called Much granules found in tuberculous material, noted the presence of virulent filtrable elements in the pus from a tuberculous abscess. The discovery of Fontes remained unnoticed until 1922, when Vaudremer found similar elements in cultures of tubercle bacilli.

Experiments in the same direction, made in Calmette's laboratory, have confirmed the fact that filtrates from tuberculous sputum or pus contain invisible elements which are virulent, leading to a typical tuberculosis. It was also noted that acid-fast bacilli are found in the lymph nodes of rabbits twelve days after an intraperitoneal injection of such a filtrate. By intravenous injection of the filtrate tubercle bacilli can be found shortly after the injection, in the rabbit's spleen.

The form under which these elements pass through the pores of Chamberland filters is unknown. Fontes' idea that the so-called "Much granules" represent the invisible elements cannot as yet be confirmed.

The "invisible filtrable virus" found in tuberculous material raises anew the problem of congenital tuberculosis. Is it possible that the "filtrable virus" passes through the barrier of the placenta leading in instances to an intrauterine infection with tuberculosis?

B. M. FRIED.

A STATISTICAL INVESTIGATION CONCERNING THE ETIOLOGY OF PULMONARY TUBERCULOSIS IN THE ADULT; RARITY OF NEW INFECTIONS; IMPORTANCE OF AN OLD FAMILY INFECTION. L. BERNARD and L. DENOYELLE, Ann. de méd. **19**:561, 1926.

Tuberculosis of the adult depends in the great majority of cases on the primary tuberculous infection. Tuberculosis contracted in the "first infancy" is practically always fatal. In the "second infancy" tuberculosis is much less fatal, but those children who survive furnish the greatest number of the adolescent and the adult tuberculosis patients. Tuberculosis contracted accidentally outside the family has "all the chances" to play a vaccinating rôle and thus lead to a resistance to subsequent infections. As contagion in the adult is not insignificant, the antituberculous fight ought to be directed essentially to the protection of infancy and to prophylactic measures in the family.

B. M. FRIED.

CHOLESTERINEMIA OF PREGNANCY IN TUBERCULOUS WOMEN. M. SALOMON and F. DE POTTER, Ann. de méd. **19**:587, 1926.

The amount of cholesterin is practically always above normal in active tuberculosis. In pregnant tuberculous women the changes in the amount of cholesterin in the blood depends on the activity of the process. In active progressive tuberculosis a slight hypercholesterinemia is present during pregnancy, followed by a decrease in the blood cholesterin after delivery. In arrested tuberculosis, the oscillations in the amount of cholesterin in the blood of pregnant women is analogous to that seen in nontuberculous pregnant women.

B. M. FRIED.

THE DIAGNOSIS OF THE PIROPLASMOSES. A. DONATIEN. THE PIROPLASMOSES OF SHEEP AND GOATS. F. LESTOQUARD. BOVINE PIROPLASMOSES DUE TO BABESIELLA [BABESIA, PIROPLASMA], WITH DESCRIPTION OF A NEW SPECIES. E. SERGENT and others, Arch. de l'inst. Pasteur d'Algérie. **4**:161, 222 and 318, 1926.

The first article contains a complete description of the laboratory methods that are indispensable in the diagnosis of piroplasmoses in beef and other domestic animals. The second article describes in detail the various forms of piroplasmoses in the sheep and goats in Algiers.

MULTILOCULAR ECHINOCOCCUS OF THE LIVER. M. L. JAHN, Beitr. z. path. Anat. u. z. allg. Pathol. **76**:1, 1926.

Jahn makes a case of the rarer multilocular form of echinococcus disease of the liver the basis of a discussion of the mode of growth of this form and of the reaction of the host tissues. As compared with the usual monocystic form of echinococcus, growth is centrifugal rather than centripetal, and the alveolar, invasive and infiltrative character of the multilocular form is due to evagination of the cuticular layer by the parenchymal layer. Associated with this form of growth is the failure of development of typical scolices. The author leaves undecided the question of possible species differences between the two forms of echinococcus. In the liver, the younger, invading cysts were surrounded by an inflammatory zone composed of leukocytes next to the cuticula, and of epithelioid cells, giant cells and lymphocytes further out. Many of the giant cells were of the Langhans type and the granulation tissue was similar to that of tuberculosis. About older cysts the granulation tissue was transformed into fibrous tissue, which had undergone hyalinization and could be distinguished only with difficulty from the cuticular membrane of the parasite. Widespread metastasis of the echinococcus had occurred to the lungs, where the growth was also multilocular. The host reaction in the lungs differed from that in the liver in that it was more acute and in places purulent. The lung involvement was held to be the result of vascular embolism.

O. T. SCHULTZ.

INULIN FERMENTATION OF STREPTOCOCCI AND PNEUMOCOCCI. E. BERGER and W. SILBERSTEIN, Klin. Wchnschr. **5**:2307, 1926.

The inulin reaction was invariably positive for pneumococci and negative for hemolytic streptococci when primary cultures were tested. Other forms were variable in reaction.

J. W. WILLEMS.

MENINGITIS TYPHOSA. A. SCHWEISGUT, Klin. Wchnschr. **6**:215, 1927.

A boy, aged 17 years, with abdominal typhoid, developed meningitis. The autopsy demonstrated a purulent cerebrospinal meningitis caused by the typhoid bacillus, which was isolated from the spinal fluid.

J. D. WILLEMS.

THE ETIOLOGY OF PEMPHIGUS VULGARIS. F. ELKE and NAGELL, München. med. Wchnschr. **73**:2067, 1926.

From the blood and urine of two patients with pemphigus vulgaris a gram-positive diplococcus was isolated which was identical with that called *Bacterium pemphigi* by Eberson.

J. W. WILLEMS.

THE IMPORTANCE OF DISPOSITION IN THE ORIGIN AND COURSE OF EPIDEMICS. R. FREUND, Ztschr. f. Hyg. u. Infektionskrankh. **106**:627, 1927.

During the spring of 1925 Freund made a careful study of an epidemic among rabbits and guinea-pigs in the animal quarters of the "Institut Robert Koch." He discovered as causative agents in all affected rabbits and in some of the guinea-pigs bacilli belonging to the group of hemorrhagic septicemias, while in other guinea-pigs the infection was caused by pneumococci or in a few cases by *Bacillus paratyphosus* B. At first glance, it appeared as if the development and course of the epidemic was due to the dissemination of the infectious bacteria and their effect on the animals, but a more careful investigation revealed that the infectious agents were incapable of producing a true infection in healthy animals, both experimentally by introduction by way of the skin, the lungs, the conjunctiva or the intestinal canal, and naturally by a close association of sick and healthy animals. It was evident that the epidemic-like infections were caused by conditions which temporarily had lowered the resistance of the animals to infection with these bacteria. The presence of such influences could be demonstrated. They consisted in exposure to low temperatures during these months. It could be shown experimentally how dangerous even a transitory injury to the mucous membranes is in the animals. By instilling a 1 per cent solution of nitrate of silver or of mustard oil into the conjunctiva or the nose, disease was produced in seven of eight rabbits which corresponded to spontaneous rabbit septicemia. The animals developed coryza and septicemia. The animal body evidently possesses strong protective mechanisms in the mucous membranes and lymph nodes at the natural points of entrance of bacteria. The micro-organisms can gain a foothold and later cause general infection only when these are weakened in some way or other. The type of infection produced in this way depends on the virulence of the bacteria which happen to be present on the mucous membranes. If virulent bacilli of the hemorrhagic septicemia group are associated with pneumococci of low virulence the former will cause the infection. If the virulence of the different bacteria is more equally balanced, mixed infections arise in which two or more bacteria participate.

W. OPHÜLS.

Immunology

STUDIES IN URTICARIA: I. WHEAL PRODUCTION THROUGH INTERNAL CHANNELS. ABRAHAM WALZER and MATTHEW WALZER, Am. J. M. Sc. **173**:279, 1927.

After the injection into the skin of serum from a hypersensitive patient, the specifically offending food is given by mouth, whereupon a wheal may develop at the side of injection. This wheal apparently simulates a constitutional urticaria.

THE BACTERICIDAL PROPERTY OF COW'S MILK. F. S. JONES and RALPH B. LITTLE, J. Exper. Med. **45**:319, 1927.

The bactericidal activity of fresh raw milk from a number of cows has been tested with the nonhemolytic mastitis streptococcus. By using this organism and other means the action of agglutinin was ruled out. The milk of all cows examined inhibited the growth of the streptococcus for definite periods. The length of the inhibition period varied; the milk from some cows prevented growth for eight hours, that of others for only from four to six hours. The inhibitory action may be as strong in the milk of a young cow in its first lactation period as in that of an old cow known to be resistant to udder infection. It is possible to absorb the streptococcus inhibitory substance by first inoculating the milk with *B. bovisepticus*. It was impossible to show that the substance was increased by artificial immunization of cows with the streptococcus. Whey obtained by the action of sterile rennet solution inhibited the growth of the streptococcus to about the same extent as the milk from which it was obtained. It is inferred that the substance originates in the udder, since it differs from blood alexin in its resistance to heat, it is not increased in the whey, although the blood proteins are more concentrated, and it is not increased in the milk when the cows are artificially immunized or repeatedly exposed to natural infection.

AUTHORS' SUMMARY.

VIBRIOS FROM CALVES AND THEIR SEROLOGICAL RELATION TO VIBRIO FETUS. THEOBALD SMITH and MARION L. ORCUTT, J. Exper. Med. **45**:391, 1927.

The calf vibrios thus far studied include one strain serologically distinct from the fetal strains. The others are closely related to the fetal strains though not identical with them. The pathogenic characters of the calf vibrios, either as possible descendents of *Vibrio fetus*, or as independent factors in the production of enteritis, have not been demonstrated.

AUTHORS' SUMMARY.

ON THE COLD AGGLUTININS IN HUMAN SERUM. K LANDSTEINER and P. LEVINE, J. Immunol. **12**:441, 1926.

The existence of two qualitatively different subtypes in group II bloods is confirmed with the method of cold agglutination. Two cold agglutinins are shown to be present in group II serums, one of these acting on blood AA^1, the other on blood AA^2. Group I bloods are characterized by the presence of a structure which is not common to all bloods, but which seems to be similar to that of A^2. Some observations made with cold agglutinins would indicate that a number of individual differences exist in human bloods, the phenomena being much less pronounced than typical iso-agglutination. From several known facts it seems probable that the individual differences such as have been demonstrated by serologic reactions are due to variations in substances other than proteins.

AUTHORS' SUMMARY.

THE SENSITIZATION OF PIGEONS TO FOREIGN PROTEINS. J. E. GAHRINGER, J. Immunol. **12**:477, 1926.

The pigeon is readily sensitized to a foreign protein as here demonstrated by the use of dog's serum. When the most favorable sensitizing and critical doses are used, a demonstrable induced sensitiveness occurs on the fourth day, increases rapidly to the tenth day and reaches a maximum by the twentieth day. It then decreases gradually to disappear between the sixtieth and seventieth

days. When single or multiple shock reactions are induced in the pigeon, each reaction is followed by a definite period of insensitiveness. The primary change in blood coagulability during anaphylactic shock is an increase in coagulability, to which a decrease in coagulability is always secondary.

AUTHOR'S SUMMARY.

ANAPHYLACTIC SHOCK AND MECHANICAL OBSTRUCTION OF THE HEPATIC VEINS IN THE DOG. J. P. SIMONDS and W. W. BRANDES, J. Immunol. **13**:1, 1927.

Mechanical obstruction of the hepatic veins of the dog produces a fall in arterial blood pressure similar to, but not so marked as, that which occurs in anaphylactic shock.

The injection of the homologous serum into a sensitized dog while the hepatic veins are mechanically obstructed does not cause an additional fall in blood pressure that can be attributed to the onset of anaphylactic shock. Peptone, on the other hand, does induce a further fall in pressure under these conditions as a result of peripheral dilatation.

When the homologous serum is injected into a sensitized dog with the hepatic veins mechanically obstructed and, after an interval of from one to three minutes, the hepatic veins are released either indefinitely, or for from fifteen to twenty seconds and then reconstricted, the ensuing fall in blood pressure is, in most animals, greater than that induced by the obstruction alone.

From fifteen to twenty seconds is sufficient time for enough of the injected serum in the circulating blood of a sensitized dog to pass through the liver to initiate anaphylactic shock.

It is suggested that in anaphylactic shock in the dog little blood escapes from the liver into the vena cava.

It is further suggested that in anaphylactic shock in the dog there is a peripheral dilatation such as occurs after injections of peptone. But before this peripheral effect is induced, the injected serum must pass through the liver of the sensitized animal, while in peptone shock this is not necessary.

THE EFFECT OF MECHANICAL OBSTRUCTION OF THE HEPATIC VEINS UPON THE OUTFLOW OF LYMPH FROM THE THORACIC DUCT. J. P. SIMONDS and W. W. BRANDES, J. Immunol. **13**:11, 1927.

Simple mechanical obstruction of the hepatic veins in otherwise normal dogs increases the outflow of lymph from the thoracic duct from 2.4 to 6.2 times, with an average increase of 5.2 times, the normal.

This increase in the outflow of lymph is almost identical with the average increase (5.45 times) observed by Petersen, Jaffé, Levinson and Hughs in anaphylactic shock, but was much less than that recorded by them in peptone shock.

Since the authors previously showed that little or no blood escapes from the liver during the height of anaphylactic and peptone shock it is suggested (*a*) that the engorgement of the liver due to obstruction to outflow of blood may be an important factor in the increased output of lymph from the thoracic duct in these two types of shock; (*b*) that this may be the chief cause in anaphylactic shock, and (*c*) that there is an additional factor, probably increased permeability of the sinusoidal endothelium, in peptone shock.

It is further suggested that the substance produced when the homologous serum passes through the liver of a sensitized dog is not entirely identical in its action with peptone. It at least seems to lack the powerful direct lymphogogic effect of peptone.

PRODUCTION OF STAPHYLOCOCCUS ANTITOXIN IN HORSES. JULIA T. PARKER and EDWIN J. BANZHAF, J. Immunol. **13**:25, 1927.

The production and titration of staphylococcus antitoxin are described.

WHAT CONCLUSIONS CAN BE DRAWN FROM THE DIFFERENT DEGREES OF THE DICK SKIN TEST REACTIONS? BELA JOHAN, J. Immunol. **13**:31, 1927.

When reading results of Dick skin tests, it is not enough to classify them only as positive or negative reactions. Differences in degrees of positive reactions must also be noted. A sharp dividing line is not present between positive and negative reactions; there are borderline reactions. The interpretation of these often depends on the physician, who reads the reaction. When these borderline reactions are numerous, a larger possibility of error is introduced.

The interpretation of the Dick skin tests is most difficult in the ages where the weak (+ positive) reactions are numerous, i. e., in the older age groups, whereas, in the first years of life (when the weak reactions are comparatively few) the readings can be made with greater accuracy.

Further studies and more experience are necessary before it can be definitely ascertained whether or not the dividing line employed at present to separate the positive from the negative reactors coincides in reality with the dividing line that separates the scarlet fever immune from the scarlet fever susceptible.

The determination of the different degrees of Dick skin reactions has a practical value in active immunization. The author found that weak positive reactors require less toxin to give an immunity, than strong positive reactors.

THE BLOOD-GROUPS AMONG THE LAPS IN SWEDEN. TORSTEN RIETZ, J. Immunol. **13**:37, 1927.

An investigation of the blood groups among Swedish Laps shows (1) a proportion of 51 per cent group I (Jansky), 42 per cent group II, 3 per cent group III and 4 per cent group IV; (2) that the proportion between I, II and III differs from hitherto examined peoples, and (3) that the examination of the blood is not in accord with observations in mongolian races.

ALLERGIC REACTIONS TO STREPTOCOCCUS ANTIGENS. GEORGE M. MACKENZIE and FRANKLIN M. HANGER, JR., J. Immunol. **13**:41, 1927.

In a high percentage of adult persons derivatives of hemolytic and green producing streptococci give rise to a skin reaction of the inflammatory type. There is wide variation in reaction to streptococcus antigens, and the authors have not been able to establish any relation between the reactions and infection.

RELATION OF ANAPHYLAXIS TO IMMUNITY. W. H. MANWARING, P. W. SHUMAKER, P. W. WRIGHT, D. L. REEVES and H. B. MOY, J. Immunol. **13**:59 and 612, 1927.

The blood of an actively immunized dog does not contain any antibody that serves as a demonstrable circulating defense to hypersensitize fixed tissues. The immune blood, however, does contain a desensitizing substance, capable of causing complete desensitization of hypersensitive fixed tissues. This desensitization is effected only after a latent period of about forty-eight hours. All phenomena of passive desensitization or passive immunization thus far studied in dogs may be accounted for as a result of the action of this desensitizing antibody. As pointed out in previous papers, there is conclusive evidence that in dogs the sensitizing antibody and desensitizing antibody are of different

chemical composition, and that neither of these substances is identical with the specific precipitin of the test tube reactions.

Tissues of actively immunized dogs transplanted by blood vessel anastomosis into hypersensitive recipients show a complete acquired insusceptibility to the hepatic anaphylatoxin. The hepatic anaphylatoxin, therefore, must be regarded as a secondary antigen, presumably of protein nature, and conceivably a denaturization product of the primary antigen. The anti-anaphylatoxic immunity factor is apparently not transferred from one animal to another by even massive immune blood transfusion.

REACTIONS OF THE URINARY BLADDER IN RABBIT ANAPHYLAXIS. W. H. MANWARING and H. D. MARINO, J. Immunol. **13**:69, 1927.

On intravenous injection of specific protein in sensitized guinea-pigs, there is a marked sharp contraction of the urinary bladder. Such contraction does not occur under analogous conditions in rabbits.

STUDIES IN HYPERSENSITIVENESS: XXIV. ON THE QUESTION OF THE IDENTITY OF THE ATOPENS OF THE POLLENS OF HIGH RAGWEED AND LOW RAGWEED. AARON BROWN, J. Immunol. **13**:73, 1927.

Experiments are described, the results of which indicate that the active principle of the two pollens is identical.

ACTIVE IMMUNIZATION AGAINST MEASLES. R. DEBRÉ, P. JOANMON and K. PAPP, Ann. de méd. **20**:343, 1926.

The blood of patients with measles was taken on the onset of the eruption and filtered, and 0.0025 cc. was diluted with physiologic sodium chloride solution, injected subcutaneously in children from 2 to 4 years of age. Fever, catarrhal symptoms and sometimes a slight eruption usually appeared between the seventh and tenth day after the infection. When 0.00125 cc. of blood was injected, a visible reaction did not occur, but on the third or fourth day leukocytosis appeared, followed by leukopenia, which was succeeded by a second leukocytosis. A second injection of 0.0025 cc. of blood was given in three weeks. Hundreds of children have been vaccinated successfully by this method without any reactions. The duration of the immunity has not been determined.

TRANSFUSION OF INCOMPATIBLE BLOOD. P. MORVILLE, Bruxelles-méd. **6**:1562, 1926.

An account of loss of blood from uterine rupture two transfusions of 300 and 500 Gm. were given from different donors with compatible blood according to direct tests. Four days later, after pain in chest and some disturbance of respiration, jaundice developed. Further tests now showed that the patient and the donors belonged to different blood groups. After death thrombosis in pulmonary vessels was found. Morville recommends that in direct tests two drops of the recipient's serum be added to six drops of sodium chloride solution to obviate pseudo-agglutination.

MESENCHYMATOUS REACTIONS. THE PARTICIPATION OF THE LUNG IN THE DEFENSE REACTIONS OF THE NORMAL AND SENSITIZED ORGANISM. W. GERLACH and W. FINKELDEY, Verhandl. d. deutsch. path. Gesellsch. **21**:173, 1926.

The rôle played by the lung in the reaction of the body against infectious material brought into the blood stream was studied. Using guinea-pigs the authors emphasize the presence of lymph follicles, of cellular and leukocytic

accumulations in the adventitia of the vessels and peribronchial tissue and of collapsed areas in the normal lung of these animals. Chicken blood injected intravenously disappeared rapidly from the vascular system of the lung (thirty minutes). Evidence of phagocytosis of erythrocytes by the endothelial cells or alveolar epithelial cells of the lung was not present. The destruction of the erythrocytes took place in histiocytes and pseudo-eosinophilic leukocytes, in the vessels of the lung, liver and spleen. In sensitized animals the injected erythrocytes were hemolyzed, a process that started immediately after their entrance in the blood and was completed after seven minutes. Participation of the endothelial cells in this reaction was not found. The animals died in shock. In desensitized animals the injected erythrocytes were also destroyed by hemolysis and with the same speed as in the sensitized animals, but shock did not occur.

W. HUEPER.

STUDIES ON THE FORMATION OF IMMUNE BODIES. ALEXANDER BELÁK and LADISLAUS CSERESZNYÉS, Ztschr. f. d. ges. exper. med. **52**:559, 567 and 572, 1926.

Intravenous and oral introduction of pilocarpin in rabbits increases the production of agglutinins, and this effect is ascribed to action on the parasympathetic nervous system. Subcutaneous injections of physiologic sodium chloride solution also increased agglutinin production, owing, it is thought, to raising tissue tensions.

CONCERNING THE MECHANISM OF INFECTION AND THE ACQUIRED IMMUNITY TO TYPHOID. W. JELIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:462, 1926.

The acquired immunity to typhoid bacilli does not depend on either the presence of bacteriolysins in the blood or the phagocytic activity of the leukocytes. The one result of the immunization is the increased phagocytic powers of the cells of the reticulo-endothelial system. Not only the bacilli are phagocytized and digested, but also the liberated endotoxins are made nontoxic by these cells.

P. R. CANNON.

THE ANTIGENIC PROPERTIES OF THE ANATOXIN OF RAMON. M. ISABOLINSKY and W. GITOWITSCH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:497, 1926.

Not the degree of precipitation, but the combining value according to the method of Kraus and Löwenstein serves as the best criterion of the antigenic properties of toxoid. Immunization experiments in guinea-pigs further confirmed this contention.

P. R. CANNON.

THE DIAGNOSIS OF LYSSA-VIRUS BY MEANS OF COMPLEMENT FIXATION WITH "KOKTOANTIGEN" AND GLYCEROL EXTRACT. R. KRAUS and J. MICHALKA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:504, 1926.

The authors find that the complement fixation reaction, using both "Koktoantigen" and glycerol extract of the brain of rabbits infected with rabies, together with immune serums, is as specific as it has been with the other filtrable viruses reported by Kraus, Takaki et al. The complement fixation reaction should be of great value in the diagnosis of rabies, especially in cases in which it is impossible to demonstrate Negri bodies. It may also make it possible to identify strains of the rabies virus.

P. R. CANNON.

STUDIES CONCERNING THE DEVELOPMENT AND TECHNIC OF THE FLOCCULATION REACTION. HUGO HECHT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:520, 1926.

This paper claims that Müller's "Ballungsreaktion" or conglobation test is identical with the author's flocculation test and only provides a new technic for the Hecht flocculation reaction.

P. R. CANNON.

SPECIFIC SKIN REACTIONS IN LEPROSY. P. BARGEHR, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:529, 1926.

The author excised nodules from patients with leprosy, and used the ones which contained many bacilli to inject intracutaneously into leprous patients in various stages of the disease. In persons who had never come in contact with leprosy, negative reactions were obtained. With persons who did not show any signs of leprosy, but who had been in contact with leprous patients for some time, positive reactions were obtained, as was also the usual case, with actively leprous patients.

P. R. CANNON.

EXPERIMENTAL STUDIES ON THE QUESTION OF THE SO-CALLED MENINGEAL PERMEABILITY. E. SINGER and F. T. MÜNZER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:532, 1926.

These experiments indicate that active immunization of man against sheep erythrocytes, as well as passive immunization with agglutinating antityphoid serum, leads to a passage of the respective antibodies into the cerebrospinal fluid.

P. R. CANNON.

METALLIC SALTS IN SERUM HORSES. H. BECKER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:555, 1926.

Becker confirms Madsen's observation that the injection of manganese chloride in serum horses increases the antitoxin content of antidiphtheria serum. The results were not so favorable in the production of antitetanic serum.

PAUL R. CANNON.

THE EFFECT OF ROENTGEN RAYS ON COMPLEMENT OF GUINEA-PIGS. ERNST ANDERSEN and EMIL EMMERICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:565, 1926.

The raying of guinea-pigs does not have any effect in changing the action of complement in the Wassermann reaction. The complement, however, is slightly increased in activity.

PAUL R. CANNON.

Tumors

HYDATIDIFORM MOLE COMPLICATED BY PERFORATION OF THE UTERINE WALLS AND SECONDARY CHORIO-EPITHELIOMA OF THE PELVIS. P. B. BLAND, Am. J. Obst. & Gynec. **13**:189, 1927.

A hydatid mole, from which the fetus was recovered, later perforated the uterus, and still later developed into a choriocarcinoma with widespread pelvic metastases.

A. J. KOBAK.

PRIMARY ENDOTHELIOMA OF CERVICAL LYMPH NODES. C. W. FLYNN, Ann. Surg. **85**:347, 1927.

Primary endothelioma of cervical lymph nodes generally manifests itself first unilaterally and progresses slowly. Visceral metastases are rare. The glands are generally firm, friable and grayish white, with a variable degree of fibrosis and softening. The lymphoid structure is lost, the gland being occupied by alveoli of large, round and polyhedral cells with vesicular nuclei and large basic-staining nucleoli. Between these alveoli compressed lymphoid cells and blood vessels are seen.

N. ENZER.

A CASE OF LEUKOSARCOMATOSIS OF STERNBERG. F. CAILLIOU and L. LOUET, Bull. de l'Ass'n. française pour l'étude du cancer **15**:363, 1926.

The report concerns a case of leukosarcomatosis in the sense of Sternberg who is of the opinion that cases of acute leukemia are of sarcomatous nature. The course of the malady can be divided into two phases; in the first period, when the patient presented herself at the clinic she showed multiple cutaneous tumors, which on histologic examination appeared to be lymphocytomas. These nodules remained for a long time localized, and were confined exclusively to the cutaneous tissue. Under the influence of radium therapy they regressed, but soon recurred with greater intensity. Changes did not occur in the hemopoietic or lymphopoietic organs.

In the second period the cutaneous nodules were accompanied by hemorrhages and fever, and also by changes in the blood characteristic of an acute leukemic lymphadenosis.

The case is of interest from the point of view of the age of the patient, which was 48 years. The disease occurs usually between the ages of 7 and 30. It is also remarkable in the initial cutaneous lesion, which is uncommon. Finally, a lymphocytoma followed by a leukemic lymphadenosis is much rarer than a myelocytoma followed by a leukemic myelo-adenosis.

B. M. FRIED.

PATHOGENESIS OF CANCER. E. KROMPECHER, Beitr. z. path. Anat. u. z. allg. Pathol. **76**:113, 1926.

Krompecher draws general conclusions relative to the origin of cancer from his previous studies of the relation of the indifferent basal cell to tumor formation. These studies were at first purely morphologic and dealt with the basal cell epitheliomas of the epidermis and later were broadened to include the tumors of mucous membranes and glandular organs, and led to his general conceptions, which are briefly summarized in this communication. The date of receipt of the manuscript by the editor is given as April 6, 1926. In view of the fact that physical suffering caused him to end his life by suicide in August, which was some months before the article appeared in print, his opening statement that what he proposes to write represents the completion of three decades of work on the subject sounds prophetic. Early in his work he drew the obvious conclusion that the proliferative potentiality which leads to normal replacement of the epithelial cells of the epidermis, to cellular replacement in regeneration, and to epithelioma resides in the indifferent basal cell. The presence of such indifferent mother cells was later postulated for the mucous membranes and the glandular organs, and from such cells there could arise hyperplastic overgrowths, adenomas and carcinomas. The varying morphology of epitheliomas and carcinomas was explained, not by dedifferentiation or anaplasia, but by the undifferentiated or indifferent character of the mother cells, which were capable of differentiation to

varying degree and along various lines, leading sometimes to metaplasia. These earlier considerations are passed in review and are correlated with the more recent knowledge of the experimental tar cancers, and neoplasia is compared with regeneration and hyperplasia. The blastogenic effect of the various accessory factors in tumor formation such as injury, inflammation, misplacement, and so forth, are considered from the standpoint of their ability to cause proliferation of the basal cells, but the most important factor is the cancer constitution, which expresses itself in predisposition to cancer. The indifferent mother cells of the various epitheliums all have as a latent potentiality the capacity for continuous proliferation. Cancer results when this potentiality is awakened into active multiplication by intracellular or extracellular stimuli. Recognition of the latent potency of normal epitheliums for continuous proliferation places the pathogenesis of tumors among the understandable biologic phenomena, and removes it from its present position as an unsolvable problem which is not to be interpreted in the light of present knowledge. What holds for the epithelial tumor applies also to all other malignant neoplasms, since in all tissues replacement of lost cells occurs from indifferent cells. There is no special tumor cell; the latter is always a descendant of a normal cell. Similarly there is no special form of blastomatous tissue growth, different from normal growth, but merely activation of the latent potency of indifferent cells for multiplication.—*De mortuis nil nisi bonum.*

O. T. Schultz.

A More Exact Knowledge of the Effect of Roentgen Rays on Carcinoma. H. Hamperl and G. Schwarz, Strahlentherapie **24**:607, 1927.

The history is given of a woman, aged 75, suffering from carcinoma in the right zygomatic region, approximately 10 by 3.5 by 2.5 cm. in size. Biopsy revealed a typical basal cell carcinoma. Half of the tumor was treated with one full dose (15 Holzknecht, 0.5 zinc, 45 minutes), the other half with one-third of this dose on three successive days. Beginning two hours after the treatment, another biopsy was done, followed by others, making a total of fifteen during a period of one year. There were two recurrences which responded finally to repeated irradiation. A comparison of their results with observations published by Alberti and Politzer on irradiated embryonic tissue seemed to show fair agreement. The primary effect of radiation is a decrease in the amount of mitosis, noticeable two hours after the first exposure, while following an interval of quiescence, the new cells were atypical (secondary effect). A treatment in this interval which is almost free of mitosis had also an effect. The amount of mitosis in a tumor does not seem, therefore, to have a bearing on its susceptibility to radiation. No difference could be noticed in the response of the growth to the full and to the fractional dose. The many photomicrographs illustrating the paper would be of interest to the pathologist.

E. A. Pohle.

Leiomyoma of the Liver. R. Demel, Virchows Arch. f. path. Anat. **261**:881, 1926.

This is a brief account of the operative removal of a leiomyoma of the liver, the tumor, which measured 11 by 12 cm., being situated at the edge of the liver near the gallbladder. Microscopically it was composed of well differentiated smooth muscle and connective tissue. Metastasis of histologically benign leiomyomas has been reported, but other tumors were not seen during the laparotomy in the case reported.

O. T. Schultz.

METASTATIC CARCINOMA OF THE SPLEEN. W. DI BIASI, Virchows Arch. f. path. Anat. **261**:885, 1926.

Di Biasi reports in some detail fifteen examples of carcinoma with metastasis in the spleen, and reviews the necropsy statistics of Lubarsch's Institute with reference to secondary carcinoma of the spleen. In 9,761 collected cases of carcinoma, the spleen was involved in 1.9 per cent. In 2,422 carcinoma necropsies in Lubarsch's Institute, the incidence was 2.1 per cent. The years 1918 to 1923 showed an increase to 3.2 per cent, as compared with 1.8 per cent for 1913 to 1917. In 62 per cent of fifty examples of splenic metastasis, the process was believed to have occurred by the blood channels, and in 32 per cent by the lymph channels. Females outnumbered males by approximately 2 to 1. The relative infrequency of secondary carcinoma of the spleen is not due to an absence of lymphatics in the pulp, but to natural resistance of the splenic tissues. Macroscopically and microscopically, carcinoma metastases in the spleen are usually sharply defined, and diffuse invasion is rare.

O. T. SCHULTZ.

INFECTIOUS ORIGIN OF CANCER. TEUTSCHLAENDER, Ztschr. f. Krebsforsch. **24**:223, 1927.

This is a critique of the infectious theory of cancer, delivered at the last annual meeting of the German Society for the Prevention of Cancer. The various types of organisms which have been proposed as causes of tumor formation and the tissue reactions produced by them are discussed, especial attention being paid to the recent work of Gye and Barnard. Although he recognizes the relation of a variety of animal and plant organisms to neoplasia, Teutschlaender concludes that the actual causation of malignant tumors by any form of living matter has not been demonstrated. He postulates four factors in neoplasia: the disposition, local or general, of the host tissues; the quality or nature of the irritant; the quantity or strength and duration of action of the irritant, and a special factor, such as the action of micro-organisms, which may act with the other factors to produce tumor in certain cases.

O. T. SCHULTZ.

ACTION OF CHLOROFORM ON CHICKEN SARCOMA. E. FRÄNKEL, Ztschr. f. Krebsforsch. **24**:252, 1927.

With dried Rous chicken sarcoma material obtained from Gye, Fränkel obtained chiefly negative results, a few inflammatory granulomatous reactions and a single spindle cell sarcoma. That the negative results were not due to the resistance of the fowls was proved by later successful inoculations with highly virulent material from another source. Treatment of the latter material with an excess of chloroform for 35 minutes at 37 C. did not decrease its virulence, and positive results were obtained with material that had been treated with 5 per cent chloroform for one hour. The inoculability of the material seemed to bear a relation to the strength of the chloroform and its duration of action, and to the amount of material treated. The author concludes that Gye's results cannot be accepted without reservations.

O. T. SCHULTZ.

IMMUNITY AGAINST A TUMOR OF THE RAT. F. REICHERT, Ztschr. f. Krebsforsch. **24**:255, 1927.

Using the bacillus which Blumenthal had isolated from a tumor of the rat and with pure cultures of which he claimed to be able to produce tumors in rats, Reichert attempted to immunize rats with the killed organism. Later inoculation

of fresh tumor tissue yielded 25 per cent of positive results, as compared with 60 per cent in a control series. Injection with dried material from the enlarged spleen of rats, which were resistant to both the living bacteria and tumor tissue, did not have any effect except a decrease in the size of the resulting tumors. When living tissues of various kinds were used for immunization, the number of successful inoculations of the tumor was reduced to 5 per cent. Since dead bacteria, dead tumor tissue and dead spleen had only a slight immunizing effect, the author concludes that the development of the resistant state is an attribute of living material used as antigen.

O. T. SCHULTZ.

PLANT TUMORS DUE TO A MOUSE CARCINOMA BACILLUS. F. KAUFFMANN, Ztschr. f. Krebsforsch. **24**:260, 1927.

With a bacillus, apparently closely related to *Bacillus tumefaciens,* which the author had isolated from mouse carcinomas, he was able to cause the formation of nodular, tumor-like hyperplasias in five of ten sunflower plants repeatedly inoculated with one strain of the organism. Other strains gave negative results. In the positive cases it was impossible to isolate the organism from the plant tumor. *B. tumefaciens* and the Blumenthal rat carcinoma bacillus gave a larger percentage of plant tissue overgrowths than the author's organism.

O. T. SCHULTZ.

CARCINOMA OF THE LIVER OF A RABBIT FOLLOWING INOCULATION SYPHILIS. VON NIESSEN, Ztschr. f. Krebsforsch. **24**:272, 1927.

In a rabbit which died three years after spontaneous recovery from syphilis resulting from the subcutaneous inoculation of human syphilitic material, the liver was the seat of a gelatinous carcinoma which apparently arose in the gall-bladder. Since many human beings with carcinoma give a history of previous venereal infection, this rabbit tumor proves that syphilis may be not merely a predisposing factor in neoplasia but also an actual causal agent.

O. T. SCHULTZ.

INCREASED PREDISPOSITION TO TAR CANCER. S. BECK, Ztschr. f. Krebsforsch. **24**:278, 1927.

The possibility of bringing about experimentally in rabbits and mice an increased predisposition to the development of epithelioma following the application of tar was investigated by Beck. The animals received repeated subcutaneous or intravenous injections of tar preparations that had been rendered nontoxic but still retained the tumor-producing property when applied locally. When animals treated in this way later received applications of tar to the skin, tumors developed in a larger proportion than in controls, appeared earlier and reached a larger size.

O. T. SCHULTZ.

TRANSPLANTABLE TUMORS OF RATS. E. BLUMENTHAL and H. AULER, Ztschr. f. Krebsforsch. **24**:285, 1927.

The authors are adherents of the infectious theory of cancer. With a bacillus isolated from rat tumors they claim to have been able to produce tumors. In a study of the distribution of the supposed virus, rats were inoculated with supposedly tumor-free suspensions of the spleens of tumor rats. One animal in each of two series of experiments developed a tumor, which was transplantable.

O. T. SCHULTZ.

ABDERHALDEN REACTION IN THE EARLY DIAGNOSIS OF TUMORS. A. SCHMIDT-OTT, Ztschr. f. Krebsforsch. **24**:292, 1927.

The author sees in the Abderhalden doctrine of protective ferments a theoretically useful procedure for the early diagnosis of malignancy. In order that the determination of splitting of the substrate by the blood serum might be as delicate as possible, the interferometer was used. In a series of 132 mice with transplantable carcinoma, sarcoma and chondroma the average reading, as determined by the method used, was higher than in normal controls. Enzymatic splitting of the substrate, when detectable, occurred early in mice and disappeared after the tumor was well developed. In rabbits with tar cancer, a difference was noted only in the later stages of the disease. In human beings with tumors, positive results were obtained in from 50 to 70 per cent. Increasing the delicacy of the reading of the reaction is held not to be of great advantage in increasing the diagnostic value of the Abderhalden reaction, because of the wide variations obtained in the series of tumor animals and human beings.

Q. T. SCHULTZ.

Technical

THE KAHN PRECIPITATION TEST FOR SYPHILIS. J. G. HOPKINS and WALKER M. BRUNET, J. A. M. A. **88**:311, 1927.

This article is based on answers to a questionary concerning the Kahn test as well as on published reports. It appears that the Kahn test is regarded as dependable, and that the Wassermann test should be used in conjunction with it. The authors summarize the results of their inquiry as follows:

The present technic of the Kahn test is superior to the earlier technic. The results obtained by the Kahn test (present technic) correspond to those of the Wassermann test, in a large majority of cases. Either test is negative in isolated cases of syphilis and positive in instances in which the serum reaction is the only evidence of syphilis. A small number of Wassermann positive serums give negative Kahn reactions. A slightly larger number of Wassermann negative serums give positive Kahn reactions. The Kahn test is somewhat more sensitive than the Wassermann in primary syphilis and more persistently positive in many treated cases. The main disadvantage of the Kahn test is its failure in a few cases showing a definitely positive Wassermann reaction. The main advantages of the Kahn test are comparative simplicity of procedure, rapidity of obtaining results, its usefulness with anticomplementary serums, and the fact that it reveals a reaction in some cases in which the Wassermann reaction is negative or doubtful.

A METHOD FOR REPEATEDLY SAMPLING THE BLOOD OF THE PORTAL VEIN IN HEALTHY ANIMALS. M. A. BLANKENHORN, J. Exper. Med. **45**:191, 1927.

In dogs a permanent cannula is inserted through which a needle may be passed into the portal vein. Of thirteen dogs the method was used successfully in eight.

ON WRIGHT'S CENTRIFUGE METHOD OF ESTIMATING PHAGOCYTOSIS AND THE RATE OF OPSONIZATION OF BACTERIA BY NORMAL SERUM. A. FLEMING, Brit. J. Exper. Path. **8**:50, 1927.

With fully opsonized bacteria phagocytosis is complete after centrifuging for one minute at the room temperature. At 37 C. opsonization is completed in a few minutes; at room temperature it takes much longer.

METHODS FOR PREVENTING THE AGGLUTINATION OF BLOOD BY GLUCOSE SOLUTIONS. W. R. PENDLETON, J. Lab. & Clin. Med. **12**:369, 1927.

Agglutination of blood corpuscles by dextrose solutions may be prevented by the addition of sodium chloride (from 0.1 to 0.2 per cent), dibasic potassium phosphate (from 0.1 to 0.2 per cent) and acid potassium phosphate (from 0.1 to 1.1 per cent), or by rendering the dextrose solution slightly alkaline (N/250 sodium hydroxide). Agglutination may be greatly diminished by the use of a definitely hypertonic solution of dextrose. An avoidance of acid dextrose solutions will diminish agglutination. The agglutination phenomenon is not specific for dextrose but will also occur with sucrose and glycerol. Agglutination may possibly be responsible for so-called "glucose reactions."

S. A. LEVINSON.

THE SEDIMENTATION RATE OF ERYTHROCYTES; THE CORPUSCLE VOLUME; AND THE ICTERUS INDEX. J. FORMAN, J. Lab. & Clin. Med. **12**:373, 1927.

A 5 per cent sodium citrate solution is run into a Sahli hemoglobinometer tube up to the 30 mark. The tube is then filled up to the 100 mark with the patient's blood. The tube is inverted several times until the citrate and blood are well mixed and the mixture is allowed to stand at a warm temperature in a perpendicular position. The time is noted. Readings of the height of the red cells are made at the end of thirty minutes and one hour. Corresponding corrections of the readings are made if the plasma is found to be slightly above or below the 100 mark. It is to be noted that the readings made are of the cell column while the European figures are for the plasma column. On this sedimented sample one makes a reading at the end of twenty-four hours to get the corpuscle volume, and then the supernatant serum, which has been diluted in an easily calculated manner, is used to determine the amount of bilirubin in the blood. From this test information can be obtained in regard to the sedimentation rate of the erythrocytes, the corpuscle volume and the bilirubin content of the blood.

S. A. LEVINSON.

THE REMOVAL OF ALBUMINS FROM THE URINE. I. ABELIN, München. med. Wchnschr. **73**:2066, 1926.

Zinc hydroxide is a simple, quick and reliable precipitating agent for the albumins in the urine.

J. D. WILLEMS.

TISSUE ELASTOMETRY FOR CLINICAL USE. H. SCHADE, München. med. Wchnschr. **73**:2241, 1926.

An instrument, the elastometer, invented for determining the degree of elasticity, softness, and solidity of tissues, is used in the diagnosis of edema, inflammatory changes, asthenia, flaccid paralysis and tumors.

J. D. WILLEMS.

SIMPLE COLORIMETRIC METHOD FOR DETERMINATION OF IODIN IN URINE. L. I. YOSHIMATSU and H. LAKURADA, Tohoku J. Exper. Med. **8**:107, 1926.

The method is based on the reduction of silver iodide dissolved in solution of potassium cyanide. The reduction is effected by sodium sulphide with development of a dark brown color. The results come on an average within 3 per cent of the actual amounts present.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, March 10, 1927

DAVID MARINE, *Presiding*

LIPOID CELL HYPERPLASIA OF THE SPLEEN IN DIABETES. LOUIS HIRSCHHORN.

The case presented was that of a diabetic patient, aged 21, with symptoms that started fifteen months before, who was admitted to the hospital in coma. The blood sugar was 0.36 per cent, and carbon dioxide was from 16 to 20 per cent. The patient died within twenty-four hours, in spite of intensive treatment with insulin, glucose and fluids.

The observations at autopsy were a marked lipemia, an enlarged liver, weighing 2,410 Gm., and a large, peculiar spleen. The latter weighed 280 Gm., and on section was a grayish yellow. The pancreas was slightly smaller than normal. The microscopic observations were interesting.

The follicles stained deeply and stood out much better than usual, owing to the presence of a thin honey-comb pulp between them. This appearance was due to the presence of an enormous number of fat-containing reticulo-endothelial cells in the reticulum. Extracellular fat was also present in this part of the spleen. The lymphoid follicles and the sinuses contained neither extracellular nor intracellular fat. The parenchyma cells of the liver had lost most of their fat and glycogen, whereas the Kupffer cells were full of these substances. Edema of the entire liver was marked. The suprarenals showed a thin glomerular layer in the cortex. The cortical fat was greatly diminished, whatever fat was present being found in the endothelial cells of the outer layers and to a lesser extent extracellularly. The pancreatic islands were greatly diminished, and the remaining ones were distorted in different ways. Some of the smaller venules of the pancreas showed recent thrombi.

About fourteen similar cases have been reviewed in the literature. They all occurred in young diabetic patients. All except one had a terminal lipemia, and with one exception, all died in coma.

The lipemia and the excessive fat content of the Kupffer cells and similar cells are interpreted as signs of a general fat mobilization. Apparently the cells of the liver and also of other tissues, but mainly the cortical cells of the suprarenals, are losing their fat, which is first taken up by the endothelial macrophages and then given up to the blood. The only tissue which has acquired the capacity of storing the mobilized fat is the splenic reticulum.

The complete absence of the physiologic lipoid in the suprarenal cortex is interpreted as a sign of cortical exhaustion. As suprarenalectomy is followed by a substantial increase of the blood lipoids, it is concluded that suprarenal cortical insufficiency might be instrumental in diabetic lipemia. The reticulo-endothelial cells play but an intermediary rôle in the metabolism of fat and are probably controlled by hormonic influences.

DISCUSSION

DAVID MARINE: I do not see the necessity for assuming a deficiency of the suprarenal cortex. In accounting for the deposition of fat in the reticulo-endothelial cells in diabetic lipemia, it seems that the deposition generally varies with the lipemia, and that the nature of the lipoids, as far as is known, is the same as that of the lipoids in blood.

I would also like to correct a statement made by Dr. Hirschhorn in connection with the work by Dr. Baumann and Miss Holly. They believe that the rise in blood cholesterol after suprarenalectomy is a terminal or premortal phenomenon. I do not think that the rise in blood cholesterol has any essential relation to the suprarenal, nor has the lipoidemia of diabetes anything to do with the suprarenal.

MAX GOLDZIEHER: I should like to mention the following facts, which will support what Dr. Hirschhorn said: In the experiments which have been recorded from the Montefiore Hospital, the rise in cholesterol was terminal, and Rothschild's rabbits died too soon after the operation. The original experiments of Chauffard involved only unilateral suprarenalectomy, and his animals lived for a considerable length of time with marked increase of the cholesterol ratio. Chauffard thought therefore that compensatory hyperfunction of the remaining gland was induced by unilateral suprarenalectomy, and he believed that to be the cause of the increased blood cholesterol. I think that the conception of an increased amount of blood cholesterol due to hyperfunction of the suprarenal is an erroneous one and contrary to the actual facts.

We recently succeeded in isolating an active principle from the suprarenal cortex in fairly pure form. This substance, when injected intravenously, even in minute amounts, produces a considerable drop of the blood cholesterol, which might be as much as 30 per cent. The drop begins within one hour after the injection, and lasts over twenty-four hours. If a substance extracted from the suprarenals wields such an influence on the cholesterol metabolism, it seems fair to say that the rise in blood cholesterol after suprarenalectomy, as confirmed recently by Jollson and Shorr, is due to the increase of that active substance.

DAVID P. SEECOF: I should like to confirm the observations in relation to the glomerular layer of the cortex of the suprarenal in diabetes; yet I cannot entirely agree with Dr. Hirschhorn. In about thirty cases of diabetes I have looked over the suprarenals carefully, and in about eighteen there was a distinct atrophy of the glomerular layer. However, in checking against several hundred other suprarenals removed from patients having other conditions than diabetes, I found the same lesions as were found in the suprarenals in the diabetic patients. In several cases showing splenic lipemia, there was no correlation between the lipemic spleens and the atrophy of the glomerular layer.

PAUL KLEMPERER: In regard to Dr. Seecof's remark, I too think that the occurrence of atrophy of the glomerular layer is not so rare. In persons 21 years of age, however, I would consider that as a pathologic condition which deserves some other interpretation than that it is incidental. I have had no experience with diabetic patients.

SHEPARD SHAPIRO: A condition simulating Gaucher's spleen can be produced readily by prolonged hypercholesterolemia. In a large number of feeding experiments that we performed we were able to simulate that condition, not only in the spleen, but also in the lung, in which there was overgrowth of these typical "foamy" cells. We found that that condition in the spleen in experimental animals is, as Dr. Marine said, more a function of the extent

of lipemia of the blood than related to a hormonic condition of the spleen itself. As far as any hormonic control of the lipemic condition is concerned, the one gland which seems to be involved more than any other, certainly more than the suprarenal, is the thyroid. If thyroidectomy is performed on an animal and an alimentary hypercholesterolemia is induced, the deposition of cholesterol occurs much more readily and extensively than in normal animals; if a partial suprarenalectomy is performed on rabbits, a small fragment of one gland being left so that the animals may live, or if a total suprarenalectomy is performed on an animal that has sufficient accessories, and these animals are then fed cholesterol, we find that they deposit the cholesterol no more readily than do rabbits with all organs intact. As a matter of fact, we found some evidence in only about three or four animals, especially in those which developed marked overgrowth of the lymphoid tissues, that such a condition in the body actually inhibits the deposition of cholesterol as compared with the animals with the suprarenals intact.

DAVID MARINE: I should like to correct a statement of Dr. Shapiro's that the lipoid in the cells in experimental lipemia is related to that in Gaucher's disease. The lipoid substance there is keratin, while in experimental cholesterolemia the substance deposited is cholesterol.

MAX GOLDZIEHER: I wish to refer to the absence of fat in the cortical cells, which is so striking when compared to the lipemia. If the storage of fat in the cells were always in proportion to the blood fat, why do not the cells of the suprarenal cortex store fat, since this is supposed to be one of their physiologic functions? I think we are dealing with changes in two tissues: first, with that of the suprarenal cortex, which has lost its physiologic capacity of storing fat; second, with that of the splenic pulp cells, which store fat in contradistinction to all the other cells. The Kupffer cells of the liver and the endothelial cells of the suprarenal cortex are the only other cells that also contain fat. The contrast between the fatty endothelial cells and the fatless parenchyma cells of the suprarenal cortex, as demonstrated on one of the slides, is particularly striking.

I think we are justified in maintaining that we are dealing with a functional disturbance of the suprarenal cortex. The glomerular layer of the cortex is practically missing, as are the lipoids of the cortical cells. There is a severe lipemia, on the other hand. Any one of these facts would not be sufficient to cause one to diagnose a functional deficiency, but all three together, i. e., the nearly total absence of both the glomerular layer and the cortical lipoids, and the presence of lipemia, indicate the insufficiency of the suprarenal cortex.

LOUIS HIRSCHHORN: It seems to me that the deposition of fat in this spleen is far out of proportion to the lipemia. There seems to be an actual hyperplasia of the reticulo-endothelial cells of the spleen. In one case reported the lipemia was not terminal. It disappeared, and the same condition, lipoid hyperplasia, was found at autopsy.

With reference to Dr. Shapiro's discussion, I wonder how old the patients were in whom the suprarenals were studied. As to the changes in the suprarenals, in most of the cases I reviewed the authors skipped over that rather hastily; they said "adrenal negative" or "no changes." I do not attempt to draw conclusions from a single case. The changes in the suprarenal were so striking that I call attention to them as a suggestion.

DAVID P. SEECOF: The ages varied; I do not remember the exact ages, but they were controlled with a similar age range.

LOUIS HIRSCHHORN: These patients were all below the age of 30; all but one died in diabetic coma. These cases form a distinct group.

ACUTE SUPRARENAL INSUFFICIENCY, SIMULATING PNEUMONIA AND CARDIAC FAILURE. IRVING SHERMAN.

A woman, aged 62, was operated on for an ulcerating epithelioma of the abdominal wall. After the operation, the patient developed a marked pallor, dyspnea and cyanosis, and the heart sounds and pulse rate became rapid. The blood pressure dropped from 150 systolic, and 80 diastolic to 80 systolic, and 40 diastolic. The pulse rate rose from normal to 180, and finally was imperceptible. Respiration rose from 18 to 45. A clinical diagnosis of bronchopneumonia and cardiac failure was made.

The observations at autopsy were mostly negative, and no evidence of bronchopneumonia could be demonstrated. The heart showed hypertrophy of the left ventricle and dilatation throughout. There was a marked atherosclerosis of the aorta and the larger arteries. The left suprarenal was enlarged and firm, and showed partly hemorrhagic infiltration and partly foci of necrosis. Most of the larger veins of the suprarenal, including the central vein, were clogged with fresh thrombi. There was hardly any intact glandular tissue in the left suprarenal. The right suprarenal was fairly well maintained, although there was a cavity which separated the cortex from the medulla, and was filled with a chocolate fluid. The cortex of the right suprarenal was hyperplastic, but did not contain much lipoid substance. The medulla was rather abundant, but showed morphologic signs of exhaustion. The musculature of the suprarenal veins was unusually thick and in no proportion to the lumen of the particular vessels.

In the absence of any other anatomic changes, Dr. Sherman said that he felt justified in ascribing both the death and the proceding clinical symptoms to the changes in the suprarenals. He interpreted the drop in blood pressure as insufficiency of the chromaffin system, while hyperpyrexia and dyspnea are ascribed to cortical insufficiency.

A number of cases were quoted from the literature which had been interpreted similarly on the basis of similar clinical and anatomic observations. A peculiar feature of the case presented was the presence of a unilateral lesion of the suprarenal. This was explained by drawing an analogy with anuria of a healthy kidney after impairment of the other one. Another analogy was the prevalence of Addison's syndrome in unilateral tuberculosis of the suprarenal.

Attention was called to the hypertrophy of the suprarenal venous musculature, which seems to be characteristic for hypertension.

DISCUSSION

DAVID MARINE: Even with one suprarenal intact, a patient may die of suprarenal insufficiency. Severe myxedema may occur when the thyroid gland is much enlarged. Dr. Sherman emphasized one thing which might be reemphasized; that is, in ordinary clinical medicine the suprarenal still plays a small rôle, and yet its importance far exceeds that of the thyroid. The postoperative reaction with hyperpyrexia may be closely related to what Kramer has spoken of as sympathetic fever, and even more closely related to the typical crisis in exophthalmic goiter.

ACTINOMYCES IN PSORIASIS. MARY A. MARCUS.

Cultures were made from the deeper layers of cutaneous lesions of psoriasis after scraping the lesions with a steel scalpel kept in 95 per cent phenol and washed in 95 per cent alcohol before use. The material for inoculation was taken on a platinum shovel previously sterilized by flame. By this technic positive cultures of a filamentous microbe were obtained in twenty-one of twenty-three cases examined, or in 91.3 per cent; this microbe was not obtained at all trials, because in many instances it was necessary to repeat the cultures from three to ten times, taking from five to thirty separate cultures each time in order to obtain a positive result. Eighteen patients presenting other dermatoses have been examined by the same culture technic without finding this microbe in any case. The name *Actinomyces psoriaticus* is suggested for the organism. Morphologically, it is not identical with any of the species of *Actinomyces* described by Drechsler.

The inoculation of this organism into the human skin and into the skin of rabbits and monkeys has produced lesions resembling those of psoriasis. There have been frequent failures, however, when the normal human skin has been inoculated. Inoculation of psoriatic patients with the living culture and with a killed vaccine prepared from it has been followed by favorable clinical results. Biopsies of skin taken from psoriatic patients have shown the presence of a branched filamentous microbe, similar to that observed in culture, in the deepest layers of the epidermis and in the interior of small vesicles near the basement membrane of the epidermis. Various problematic bodies have also been seen in these tissue sections in all three stages: acute, subacute and chronic.

DISCUSSION

ANNA W. WILLIAMS: The question of the microbic cause of psoriasis has long been an unsettled one. If, as Miss Marcus claims, her organism is obtained with such difficulty that many attempts must be made before she gets a positive result, this may account for the irregular results obtained by other workers. There are analogies in other conditions, such as lupus or blastomycosis. It is well known that unsuccessful attempts have been made to obtain cultures from certain blastomycotic lesions. The organism once isolated from such lesions may be grown with more or less ease, but many attempts must be made before primary cultures can be obtained, if they can be obtained at all. It is interesting to know that the type of organism that Miss Marcus found in psoriasis — *Actinomyces* — is related to both these groups, i. e., to tubercle bacilli and to blastomycotic organisms. We must remember, on the other hand, that organisms belonging to the *Actinomyces* group are relatively frequent in nature, and that therefore controls of the culture work should be extremely rigorous. Miss Marcus' technic in making cultures seems complete, but I have not been able to follow it step by step, and either one has to be sure for himself that such organisms develop in the right culture mediums from a significant number of lesions, or else there must be corroboration from other trustworthy workers before one can be satisfied that all the essential controls have been used. I have examined many of her sections, and have found them well done. The sections show without doubt many more or less definite granules and the threads which might be the organism, but in only one series have I seen morphologically definite organisms. This of course is not strong evidence in favor of this organism being of etiologic significance. It is interesting enough, however, with the other claims made by Miss Marcus, to emphasize the necessity for further work.

WARD J. MAC NEAL: I think that Miss Marcus has the sort of enthusiasm and industry that we all should emulate in carrying on research. I wish I could say as much in regard to the critical attitude which the research worker should preserve toward his work for his or her own good. However, I think you will often observe that in those cases in which the enthusiasm is great, perhaps the critical attitude toward the work is not so highly developed. Personally, I feel confident that there are certain facts in this work which promise a great deal. As far as settling the problem of etiology of psoriasis is concerned, I feel sure we are far from that. The work is still, to my mind, in a relatively early stage. I might point out that as long ago as 1885, Lassar demonstrated, at the Berliner medicinsche Gesellschaft, rabbits in which skin lesions had developed following inoculation with material from psoriasis. He stated, and to my mind correctly, that in some rabbits it is possible to induce skin lesions exhibiting striking resemblance to psoriasis by the use of material from lesions of human psoriasis. The lesions he produced were large, from 10 to 15 mm. in diameter, showing the characteristic superficial scaling. When these scales were removed, there was a marked tendency to bleed. There was also loss of hair over the surface such as one observes in human lesions. Yet he was willing to say only that these lesions showed a remarkable resemblance to psoriasis. I would commend the attitude of this observer to all who have to do with the interpretation of lesions in animals in relation to human disease. We should not neglect, however, to attach some importance to observations of this sort. Lassar was able to perform this kind of experimentation on several occasions, and he said that four years before he had demonstrated to Virchow and Salkowski similar lesions in rabbits.

In 1919, Bory favored the parasitic theory of the etiology of psoriasis, and in his paper he described the study of a case in which the disease developed under his observation. The patient came to him for itching lesions of the skin, and while the patient was under treatment, psoriasis developed in these lesions. Bory proceeded to study the fresh lesions by scraping them and subjecting the material to microscopic examination. In these scrapings he was able to find branching filaments, extremely fine, which he put into the group of *Oospora* (*Actinomyces*). He made large numbers of cultural attempts, with results which he interpreted as negative, as he was unable to distinguish possibly positive cultures from accidental contaminations. The work was done under war conditions, and the technic was not regarded as above criticism. These two observations are fundamental for experimental work on psoriasis. The observation of the production of psoriasis-like lesions in rabbits by Lassar is of great importance.

As far as the results of the culture work of Miss Marcus are concerned, I am able to verify the observation of branching filamentous microbes in these cultures, but am unable to state whether or not they come from lesions of psoriasis. They have been taken by a technic that attempts to avoid other sources, but at the same time one cannot be sure that contamination has been excluded.

Concerning the production of the disease, psoriasis, by inoculation of these cultures, it seems to me that the evidence is wholly lacking, as far as our own observations are concerned. I am willing to grant that by the inoculation of human skin in cases of psoriasis, it is possible to produce lesions similar to those already on the skin, but this can be done by mere injury to the skin without inoculation of any kind. A person who has psoriasis develops lesions as a result of minor injuries to the skin, so that in respect to the production of

the disease by inoculation of the microbe, this evidence is not in the category of proof that the bacteriologist ordinarily requires.

The question of the production of psoriasis in persons who do not suffer from this disease is extremely important. I have not been able to observe any instances in which the disease has been experimentally produced in the human being, and I have been able to observe intimately one person in whom this was tried, so that I feel that in that particular instance the result certainly was negative. This does not prove anything, but is merely a negative result. We know that we can take material directly from a psoriatic person and inoculate it into the skin of a healthy person with a negative result. We are left in doubt, which is the proper attitude of mind.

In regard to the production of these lesions in animals, I might mention that Lassar pointed out certain characteristics in his lesions. They appeared in the third week after inoculation, and continued to progress and extend; they became red at the base, and large scales were produced. The lesions I have seen in animals have not approached such an appearance. Of course I should hesitate to make a diagnosis of psoriasis in the human being as far as experimental skin lesions are concerned, preferring to let the decision rest with the expert dermatologist; but when it comes to animals, I know perfectly well that I cannot make a diagnosis; so it seems to me that these inoculation lesions in animals leave us in a somewhat doubtful state.

In regard to the treatment, this is of tremendous importance to the clinician. When a person with psoriasis, who has been treated by one physician after another, at many clinics and in many countries, is cured in this fashion, he is much impressed. That is something, but I think that every scientist and every pathologist takes the view that the results of treatment are of no value as evidence of etiology. Patients get well, get worse, die and improve on the same treatment. When people are sick they must be given treatment, but what happens to the patient as the result of this treatment is not of much scientific value as evidence of etiology.

A. Schuyler Clark: I have been extremely interested in Miss Marcus' work on psoriasis. These patients have come from my clinic at the Post-Graduate Hospital, and I have had an opportunity from time to time of seeing the therapeutic results. These results in some cases have been striking. I referred to Miss Marcus a private patient who has had a severe case of psoriasis for a great many years. I have seen this patient with her hands entirely involved, unable to dress or bathe herself. There were lesions on the face and all over the body. While this patient has been under treatment, she has improved markedly. The psoriatic lesions have lost their infiltration. The lesions have broken up. There is no scarring in the centers; the scales have disappeared. The erythema still remains. There is pigmentation left where some of the lesions have entirely disappeared. However, I think Dr. Mac Neal emphasizes an important point about therapy in disease, and I think it is particularly referable to psoriasis. We all know that psoriasis often disappears spontaneously for a greater or less length of time, and we know that it disappears and apparently does not recur. It is called an incurable disease, but I have seen patients who have been well for fifteen years, so that indicates that psoriasis can be spontaneously cured. A feature of the therapy is that apparently there is little or no improvement, especially when patients are in the chronic stage under two or three months. The patient to whom I referred apparently felt no improvement from inoculations and injections until after four months. She has shown improvement now for a period of two months, and says that she thinks she can notice improvement after each treatment;

so that while there has been clinical improvement in a number of these patients, we must be careful in ascribing that to the therapeutic inoculations. I am interested in having Miss Marcus go on with her work. There have always been two schools of opinion concerning the etiology of psoriasis. One is the so-called local school; this group believes that the lesion is of parasitic origin. Other dermatologists believe that psoriasis is a metabolic disease. If Miss Marcus can fulfil all of Koch's postulates, if she can inoculate even a few nonpsoriatic patients and produce lesions of psoriasis repeatedly, I think we must begin to think she may have found the causative agent. I think one fact to be brought out is that in a psoriatic patient a scaly lesion resembling psoriasis develops after scarification, but if at the same time Miss Marcus is giving these patients an injection of her vaccine, there is certainly less tendency for these patients to develop a scaly lesion at the site of the scarifications. We all know that injury to the skin of a psoriatic patient tends to produce a psoriatic lesion, and it would seem apparent that in some cases the vaccines have tended to prevent the formation of scaly psoriatic lesions at the point of scarification. Pain usually follows the use of vaccines, and occasionally the tissues break down at the site of vaccination.

PAUL KLEMPERER: I should like to know whether attempts were made with the same careful methods to isolate the same organism in other skin conditions.

J. GARDNER HOPKINS: Did Miss Marcus describe the exact mediums she has used and the method of cultivation? It seems to me that the first thing in confirmation of this work should be the demonstration that the organism is present in psoriasis with some constancy. I think it would be extremely interesting if Miss Marcus is ready at this time to publish the exact method so that others might make an attempt to confirm the work.

LOUIS GROSS: I think it is important to point out that even if Miss Marcus can repeatedly find this organism in the lesion, and if it is confirmed by others, it is still necessary to make sure that it is not a secondary contamination. The question of therapy has properly been raised by Dr. Mac Neal, and one knows that a nonspecific milk preparation and other foreign proteins can cause a regression of psoriatic lesions, so that an observation that vaccination with these organisms causes a regression of the lesions might still mean nothing as to the specificity of this agent. Miss Marcus should make studies on the immunologic phenomena of the serum from these persons in relation to pure cultures of her organism, and she should try to reproduce the lesion with filtrates in nonpsoriatic patients. She should try filtrates to make sure that *Actinomyces* is not an accidental contaminant.

MARY MARCUS: In regard to the reproduction of lesions in animals, I have made controls with organisms other than *Actinomyces*, and none of them developed a typical psoriatic lesion similar to that which was developed by the inoculation of *Actinomyces psoriaticus*. For a control, inoculations were made in an animal with a fungus recovered from a patient with nodular skin lesions; these inoculations were made side by side with the inoculations with *Actinomyces*. The latter gave rise to a lesion similar to psoriasis, while the former gave rise to an actual nodule. I have tried many other organisms as controls, and all have given negative results. With the *Actinomyces* scarifications and dermal sac inoculations I have succeeded in reproducing lesions similar to those of psoriasis in one monkey and in five rabbits, and in two nonpsoriatic patients. One of the latter had a case of dermatitis herpetiformis.

The question of Lassar's work is rather interesting. I have studied his work carefully and also have had the opportunity to discuss the same with

Dr. Jay F. Schamberg who was personally present on the occasion when the demonstrations of Lassar's animal work were made. Some were of the opinion that the lesions were similar to those of psoriasis, but others were not willing to diagnose them as psoriatic lesions.

The lesions that Lassar reproduced appeared different from those I have reproduced. His animal lesions were larger and showed more marked scabbing, and bled more freely after the scab or scale was removed than those that I reproduced. The latter consisted of small, circumscribed, infiltrated papules covered with characteristic white, silvery scales similar to the psoriatic lesions. To my mind, it seems therefore that the fine, silvery scale observed is of far more significance than the size and the bleeding of the lesion when the scab is removed. The significance as to whether or not there is a loss of hair is rather doubtful, for in all the instances I have had occasion to observe, in areas in which the lesion was in human psoriatic patients, the hair was intact. We also must bear in mind that Lassar inoculated the material obtained directly from the psoriatic lesions, which of course might have had secondary invasions resulting in more extensive lesions which bled more freely after the removal of the scab. On the other hand, the inoculations I have made were of the pure culture of *Actinomyces* isolated from the lesions of psoriasis, and the site of inoculation was protected with a shield, so that there was less chance for secondary infection. However, Dr. Schamberg grafted a lesion of psoriasis into his skin and obtained negative results. Destot, on the other hand, apparently successfully inoculated himself with a postvaccinal psoriatic lesion from a baby. We can, therefore, infer that the products from a psoriatic lesion may give rise to psoriasis, but it seems to me that the successful production of a psoriatic lesion with a pure culture of a micro-organism isolated from a specific source is of far more significance.

Furthermore, I wish to bring out that only two of four human volunteers were successfully inoculated with specific *Actinomyces* after three trials.

I fully agree with Dr. Mac Neal's statement that psoriatic lesions in the psoriatic person can be induced by mechanical injury, but, on the other hand, I have found in many instances that the inoculation of the psoriatic person with the micro-organism failed the first two or three times it was tried. The person whom Dr. Mac Neal was able to observe was inoculated only once, and therefore it is not conclusive proof that that person might not have developed psoriasis if he had been inoculated persistently in the same manner that I inoculate psoriatic patients.

As to the question whether or not psoriasis is a parasitic disease, it occurs to me that the very fact that psoriasis has a quiescent stage and an active stage and disappears spontaneously seems to infer that it is of a parasitic nature; for example: during the active stage, in the course of treatment, improvement usually takes place within two months or so, and then the lesions gradually disappear. We know, as I have previously stated, that psoriasis spontaneously clears up without treatment. By treating patients according to the method described, dermatologists might obtain evidence answering the question as to why psoriasis suddenly clears up. It thus may bring to light an immunity effect, that is, that during the active stage antibodies are probably developed in sufficient numbers to overcome the toxin. For the same reason, owing to the production of antibodies during the active stage, the quiescent stage results or the lesions entirely disappear spontaneously.

As to the question of Dr. Klemperer, I have been studying fifteen other cases of different dermatoses under the same modified method, but have tried each only once; none showed the filamentous micro-organism *Actinomyces*.

In answering Dr. Hopkins' question, I wish to state that the method is primarily given in the previous report, in which also some of the culture mediums are given. A few modifications are suggested in the present paper.

I wish to ask all the co-workers in psoriasis to offer suggestions and information as to the difficulties encountered in reproducing the disease in nonpsoriatic patients. Fifty per cent of my inoculations in nonpsoriatic patients were unsuccessful. Of course this might account for the fact that the person inoculated must have a special susceptibility for psoriasis, but it would be interesting if we could detect this susceptibility beforehand. I shall therefore endeavor to establish a test for that purpose, one which would be generally useful as is the Schick test.

ERYTHROBLASTOSIS, "KERNIKTERUS," AND CONGENITAL HYDROPS. ALFRED PLAUT.

The relation between erythroblastosis and congenital hydrops has been known since 1910 when Schridde published the pathologic observations in his cases. This disease is named Schridde's type of congenital hydrops in contradistinction to general edema from other causes. To call it erythroblastosis seems inadvisable since this anomaly of the blood might be found in other conditions without hydrops, but a better nomenclature which describes the chief features of the disease is fetal hydrops with erythroblastosis. In 1921, von Gierke saw pathologic changes as described by Schridde in a nonhydropic baby with "Kernikterus." He established the hypothesis that these diseases might be related; they might represent different complexes of symptoms which nevertheless are due to the same noxa. The familial occurrence of both diseases also impressed him.

In the literature several families are described in which hydropic babies were born after the previous early death of children with or without jaundice. As far as our knowledge goes, there are no reports of the occurrence of both diseases in one family as shown by pathologic observations. We are able, by furnishing such a report, to support von Gierke's hypothesis. The first case has been published previously by Dr. Bullard.

The mother, whose personal history is irrelevant, had her first child at the age of 19. The child was normal. Five years later she again had a normal pregnancy and was delivered of a normal baby. On the day after delivery the baby became jaundiced; the following day, in spite of deepening of the icterus, the baby still did not seem sick. One day later, however, he suddenly became ill, with rapid increase of the discoloration, and died. Autopsy was not performed. The mother soon became pregnant again, and was delivered of a normal baby who, however, died suddenly within one hour on the fourth day; there is no statement as to whether jaundice was present or not. Autopsy was not performed. Seven months later the fourth pregnancy began. In the seventh month of this gestation the uterus enlarged rapidly, attended by edema of the feet, nausea, insomnia and discomfort. The urine and blood pressure were normal. At the end of the eighth month a hydropic baby was born. After the head was delivered by forceps, the abdomen was so swollen as to offer considerable difficulty to the obstetrician. The observations at autopsy were those of the Schridde type: an enlarged liver and spleen with many myeloic, chiefly erythroblastic, foci.

The blood picture could be studied from the contents of blood vessels in the paraffin sections. The blood showed numerous erythroblasts. The liver and spleen showed hemosiderosis. Pigment, which partly gave a positive iron reaction, was present in the convoluted tubules of the kidneys. Smaller myeloic

foci were found in the intestine, visible to the naked eye as hemorrhagic spots. The edema was intense; no jaundice was present; the bile was thin and slightly milky. The thymus gland was small. The heart was hypertrophic. Thus the case is diagnosed as a classical Schridde's type of fetal hydrops with erythroblastosis.

The woman, who always recovered well after the deliveries, became pregnant again two years later. A male child was born. The mother and baby were in excellent condition. After twenty hours, jaundice of the baby was noticed, but he nursed well. On the third day he became restless, stiff and listless. He died on the fourth day with an agonal rise of temperature. The hemoglobin was 92 per cent by the Sahli method; there were 4,580,000 red cells and 49,000 white cells; 51 per cent of the leukocytes were polymorphonuclears; 6 per cent myelocytes; 23 per cent lymphocytes; 11 per cent mononuclear cells; 5 per cent eosinophils, and 4 per cent mast cells. About 1 per cent of the erythrocytes were nucleated, or 45,000 per cubic millimeter. Most of them were medium sized polychromatic normoblasts; some were larger, orthochromatic ones of different sizes, with free nuclei, mitotic figures, but no true normoblasts were found. Among the erythrocytes the polychromatophilia was more marked than the anisocytosis. Unfortunately no van den Bergh test of the blood serum was made. The coagulation time was three minutes on the second day of life. A report states that the urine sediment consisted of urates.

Autopsy showed intense jaundice and no edema. Only the scrotum was swollen. The skin was homogeneously dark greenish yellow; the sclerae were yellow. The bile ducts were normal; the bile was olive colored. It was thin but viscid. The papilla of Vater was normal. None of its surroundings were swollen. The liver weighed 205 Gm. (instead of 150); the cut section was purplish with a brownish-yellow hue. The cross-sections of some small bile ducts appeared as green dots. The liver was slightly firmer than normal. The relation between the different lobes was normal. The spleen weighed 52 Gm. instead of 11; it was slightly firmer than normal; the cut surface was homogeneous, purplish and slightly waxy; no follicles could be seen. The brain substance was pale and slightly edematous. The nuclei in the brain and medulla were yellowish green, in striking contrast to the surrounding tissue. The nucleus ruber showed the darkest color. The choroid plexus was normal; the hypophysis also was normal. The amount of fluid in the ventricles was slightly increased; the fluid was colorless. There was no jaundice of the cartilage.

The microscopic pictures of the liver, spleen and kidneys were essentially the same as in the first case. The pigment in the convoluted tubules of the kidney was mostly so fine that the single granules could not be seen even with the oil immersion. The iron reaction accordingly gave a diffuse bluish-green color to the cytoplasm. In the first case the pigment had coarser granules, and only part of it gave a positive reaction; such differences, however, are reported in the literature on congenital hydrops.

Thus the assumed connection between the two diseases obviously exists. It is true that the new-born child has a tendency to react with myelotic change on different stimuli, but the syndrome of erythroblastosis, hemosiderosis in the liver, spleen and in part of the kidney, often accompanied by smallness of the thymus gland, seems characteristic enough to draw the conclusion of a close relationship. I have little doubt that autopsies of the babies in icterus gravis familiaris and of the nonhydropic babies of women who have given birth to hydropic ones would reveal more instances of "Kernikterus" and

give more evidence of the connection between fetal hydrops, erythroblastosis, icterus gravis familiaris "Kernikterus" and other forms of jaundice in the first days and weeks of life, including the exceptional cases of congenital jaundice. It is to be hoped that such a study will throw more light on the problem of icterus neonatorum.

DISCUSSION

DAVID P. SEECOF: What were the sexes of the children? Was there any predominance of either?

ALFRED PLAUT: Yes, the male.

DAVID P. SEECOF: How about the father?

ALFRED PLAUT: There are cases in which the mother has first been married to one man and has had healthy children, and then with another man has had children with fatal jaundice; but the reverse is also found, namely a man's first wife has had a healthy child, and his second wife has had a jaundiced child. I would not conclude anything concerning the factor of sex. It might be satisfying to think that there might be something in the hormonic source, but after seeing that rupture of the spleen in typhoid fever occurs practically always in man, and that congenital malformations of the heart are especially frequent in males, while the isolated patency of the botallian duct is found chiefly in female babies, I have stopped drawing conclusions from sex distribution as to hormonic sources.

PAUL KLEMPERER: This is the first time that the familial icterus gravis of the new-born child has been connected with erythroblastosis, "Kernikterus" and congenital edema. Some years ago I reviewed the literature on that subject, and, as far as I can recall, in none of the reports was mention made of edema. "Kernikterus" was found mostly in cases in which a careful autopsy was performed. The observation of Dr. Plaut is most interesting. Was there a marked erythrophagocytosis in the spleen and the liver? In cases of icterus neonatorum which I had occasion to study the most remarkable erythrophagocytosis was found. Erythrophagocytosis in the spleen and liver is a rather common finding in premature children as well as in full term new-born children. The marked degree present in icterus neonatorum suggests that the jaundice is only an exaggeration of a physiologic form of icterus disposition (Ikterus-Bereitschaft of Hirsch and Yllpo). If erythrophagocytosis was not a symptom in this case, it does not conform with von Gierke's observation in which erythrophagocytosis was a conspicuous factor. Von Gierke even tried to explain the severe icterus in his case as being due to increased destruction of red blood cells.

DAVID P. SEECOF: I was not thinking of the gonads in these cases, but the possible relationship of these diseases to hemophilia. I am not familiar with the literature, but it seems to me that the jaundice may be related to the destruction of the blood cells and suggests a possible relation to the hemophilic group of familial or congenital disease.

ALFRED PLAUT: In relation to the hemophilia, I did not see any, and I could not find any reported in the literature.

There was no marked erythrophagocytosis in our cases. I received the impression that there are many transitions between icterus neonatorum which might be familial also and this so-called icterus gravis. Icterus gravis neonatorum as a well described clinical and anatomic entity is a goal from which we still are far away, and I can only repeat that many well observed cases are necessary before we can attempt to make a good classification of these diseases.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, March, 14, 1927

LLOYD ARNOLD, *President, in the Chair*

A FIBROMYXOMA OF THE ENDOCARDIUM. EUGENE F. TRAUT.

A retired merchant, aged 76, an inmate of the Versorgungsheim der Gemeinde Wien, had a condition diagnosed clinically as cerebral apoplexy. There were no symptoms of cardiac insufficiency, and he died thirty-six hours after the hemorrhage. The anatomic diagnosis (Professor Jacob Erdheim) was hemorrhage into the left hemisphere with rupture into the ventricles. The heart changes were incidental and played no part as a cause of death.

Fig. 1.—Photograph of the tumor in situ.

The external appearance of the heart was normal. A longitudinal incision through the left side disclosed a pedunculated round tumor as large as a small hen's egg attached to the upper border of the foramen ovale and hanging into the left auricle (fig. 1). Its greatest diameter was 4.5 cm., and the pedicle attaching it to the septum atriorum was 2.5 cm. thick and 1 cm. long. The tumor was dark red with patches and streaks of yellow on the sides. The pedicle was gray. The surface most distant from the pedicle was roughened. There the tumor had a fibrinous attachment to the opposite wall of the auricle. At the attachment of the pedicle, the septum was 1 cm. thick. Palpation of the tumor gave the sensation of a bag filled with pebbles. It was so flabby that on a flat surface it flattened out. Not far from the base of the tumor was a firm, gray prominence 4 mm. wide and about 3 mm. high, roughened with fibrin.

The wall of the left auricle was moderately hypertrophied. The heart had no other gross abnormalities. There were no scars or mural thrombi. On

cut surfaces the mass had a red and yellow mottled appearance as noted externally. Sections taken from several parts were stained with hematoxylin and eosin, van Gieson's stain, Weigert's stain for elastic tissue, the Berlin blue stain for iron pigment and the Unna-Pappenheim stain for plasma cells.

The mass (fig. 2) consisted of edematous connective tissue with small middle-sized vessels consisting of endothelium alone and occasionally a small layer of elastic tissue. Hemorrhages were scattered here and there. The distribution of hematogenous pigment was more extensive. There were great collections of phagocytes filled with hemosiderin. Spindle cells were infrequent, and those present did not contain pigment. The cell bodies were absent in

Fig. 2.—Section from the interior of the tumor (hematoxylin and eosin) showing the loose connective tissue structure, phagocytes filled with hemosiderin, and plasma cells.

many places, but the fibrils persisted. Meyer's stain for mucin failed to give a positive reaction anywhere in the tumor. Hyaline degeneration was present in many places. A considerable part of the mass was made up of infiltrated cells, lymphocytes and plasma cells occurring separately or together. In the most extensive regions of infiltration, the lymphocytes were crowded into the center. The plasma cells lay along the periphery. Among them were numerous Russell bodies, additional evidence of a chronic inflammation. Hemosiderin accumulations were especially marked in the vicinity of the infiltrations. Small deposits of calcium were present in the hyalinized regions.

The elastica stain demonstrated that the tumor contained much elastic tissue. The elastic fibers were irregularly divided and were especially thick near the surface and surrounded the larger vessels. Elastic fibers also enclosed round and oval masses of mononuclear cells in the interior. The shape of these cells varied, corresponding most nearly to lymphocytes and plasma cells.

A thick layer of hyalinized connective tissue, with scattered regions of calcification formed the surface of the tumor. Only in the pedicle did elastic tissue form the outer layer of the tumor.

The appearance of the septum varied with the part examined. In one place the endocardium was slightly thickened and infiltrated with lymphocytes and plasma cells as well as a few wandering cells containing pigment. The myocardium underneath had a moderate amount of fibrous tissue, infiltrated with lymphocytes and plasma cells.

In a place not far removed, the endocardium was markedly thickened; there was hyaline degeneration but no infiltration. In another place the endocardium was covered with a white thrombus, and at one place the fibrin was 3 mm. thick, hyalinized and partly calcified. The free surface of the thrombus was covered with a layer of fibrin containing red and white corpuscles. In contrast to the appearance of the pedunculated mass, the organization of this thrombus had progressed very little by infiltration with a few spindle cells, but without vessels. The thrombus had no elastic fibers in spite of its attachment to the elastic endocardium. The myocardium contained a small amount of fat. Both the endocardium and the myocardium seemed to extend a short distance into the pedicle of the tumor.

Tumors of the endocardium are uncommon. Most often they are like the one described, being fibrous, pedunculated structures arising from the soft fibrous tissue in the subendothelial layer of the endocardium, and then usually occur in the auricles. More have been described on the left than on the right side of the auricular septum. The margin of the foramen ovale is a favorite site of attachment. Of course, congenital anomalies are common in this region. Berthenson (*Virchows Arch. f. path. Anat.* **132**:390, 1893) and after him Albrecht considered these growths among the malformations, structures arising from fetal rests.

Forel and others regard them as pseudoneoplasms. Forel considered them simply organized thrombi, pointing out that they occur in the auricles, the favorite site of mural thrombi. According to Forel and his followers, the connective tissue fibers are the organizing tissue.

Against this view and in favor of the neoplastic origin of the growths is their flabby consistency and the lobulation. A thrombus as large as these tumors could never be organized through a narrow pedicle. An organizing or organized thrombus contains at least in parts, deposits of fibrin, usually hyalinized. Fibrin is absent in my tissue except for a thin layer on the capsule. The buffeting in the blood current explains the hemorrhages in the interior of the tumor. Elastic tissue is rare in organized clots but abundant in the sections of this mass. Endocardial tumors usually are found accidentally during postmortem examination. Among their commonest manifestations are multiple emboli in the systemic circulation. I believe that this pedunculated mass of the left ventricle is a tumor.

DISCUSSION

EDWIN F. HIRSCH: There is a close resemblance between this tissue and tissue of inflammatory origin. The genesis of this mass may be like that of nasal polyps.

E. F. TRAUT: Professor Erdheim considers the mass to be a tumor.

CHANGES AT THE ORIFICES OF THE INTERCOSTAL ARTERIES IN A DISSECTING ANEURYSM OF THE AORTA. N. F. FISHER. (From the Norman Bridge Pathological Laboratory of the Rush Medical College of the University of Chicago and the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago.)

A report by Crowell (*J. A. M. A.* **77**:2114 [Dec. 31] 1921) contains a review of dissecting aneurysms of the aorta and records four more. In an analysis of 215 such aneurysms, he states that in more than 90 per cent the changes were either marked fatty and fibrous plaques or advanced sclerosis with ulceration. In about 9 per cent these alterations were slight. The age of most of these patients is 40 years or more, but it ranges from 13 to 95 years. The ascending portion of the aorta was involved most frequently and other parts of the aorta in order with decreasing frequency.

The primary rupture is of the intima. This may extend through most or all of the media, because the dissection occurs between the media and the adventitia, or in the outer layers of the media. The branches of the aorta may be dissected or even cut across at their origins. The pressure on the branches of the aorta may cause marked circulatory disturbances. Crowell says that little attention has been given to such interference of the circulation, a disturbance which alone may cause symptoms. Disregard of these symptoms may be responsible for the failure to recognize dissecting aneurysms of the aorta during life.

CASE 1.—A woman, aged 64, was admitted to Washington Boulevard Hospital (S. R. Slaymaker), May 5, 1926 at 1:45 p. m. She complained of severe pain in the region of the heart and between the shoulders. The temperature was 98.8 F., pulse rate 80 and respiration 20; the heart was enlarged and the beat irregular but without murmurs. After morphine and a digitalis preparation were given, the patient slept and was fairly comfortable. At 9:00 p. m. she complained of a severe pain between the shoulders; she died after twenty-five minutes.

Necropsy (R. D. Evans).—Syphilitic sclerosis and dissecting aneurysm of the aorta; left hemothorax; compression atelectasis of the left lung; blood staining of the tissues of the posterior part of the mediastinum; detached parietal pleura of the upper part of the left pleural cavity; slight bilateral passive hyperemia and edema of the lungs; fatty changes of the pulmonary arteries; cyst of the left ovary; multiple calcified fibromyomas of the uterus; calcified peribronchial lymph node (healed tuberculosis?); right fibrous pleuritis; coal pigmentation of both lungs; diverticula of the jejunum; polyp of the cervix uteri; cholecystocolic ligament.

The aorta was 63 cm. long. The lining of the first 10 cm. was smooth, except for a large irregular, yellow, elevated plaque 2 cm. in diameter and a few similar ones, as large as 5 mm. in diameter. The lining of the aorta elsewhere was roughened throughout by irregular plaques or wrinkled, ulcerated and eroded regions. There was a transverse slit 1 cm. in length, 2 cm. distal to the root of the innominate artery. A similar transverse opening 1.5 cm. long was noted about 1 cm. further. Both openings extended through the intima and the media to communicate with an aneurysmal sac. A probe could be passed distally between the coats of the aorta for several centimeters.

Beginning at the upper border of the junction of the innominate artery and the aorta, there was a dissecting aneurysm which involved the entire circumference of the aortic wall for a distance of 8 cm. In the next 13 cm., the aneurysm was from 2 to 3.5 cm. wide and involved the left intercostal arteries

and in the next 9 cm. down to the renal arteries, the entire circumference of the aortic wall was dissected, except for a narrow region about 6 to 10 mm. wide on the posterior wall. One centimeter proximal to the opening of the superior mesenteric artery was a transverse slit 0.9 cm. wide, surrounded by an atheroma which connected the intramural space with the lumen of the aorta. There were several small blood clots here. Adherent to the wall of the aorta, just below the innominate artery was a mass of mediastinal fat and a sac, communicating with the intramural space in the aorta. The sac contained freshly clotted blood.

All of the intercostal arteries were present, except the eighth on the left side which probably was congenitally absent. A 2 mm. probe could be passed into each intercostal artery. The lumen of each of the arteries on the left side was reduced in size, especially of the second, third, fourth and sixth intercostals, whose lumen was reduced to 1 mm. or less. The lumen of the first, second, third, fourth and ninth intercostals on the right side was reduced, especially of the fourth and ninth arteries. The aneurysm surrounded the first, second, third, fourth and fifth intercostal arteries on the right side, and all on the left.

Histologic sections were taken transversely to the intercostal arteries at their junctions with the aorta. These were made at different levels to determine the extent to which the different layers in the walls of the intercostal vessels were involved as well as to estimate the size of their lumens.

Dickenson (*Tr. Path. Soc. London* **13**:48, 1862), McCallum (*Bull. Johns Hopkins Hosp.* **20**:9, 1909), Barhat (*Arch. Heilk* **13**:473, 1872) and Todd (*Tr. Med. chir.* **17**:301, 1844) have reported cases in which certain paralyses could be explained easily on the basis of interference with the blood supply to the spinal cord. In others, as those of Adami (*Montreal M. J.* **24**:945, 1895) and Edwards and Stone (*Tr. Path. Soc. Philadelphia* **6**:38, 1878) a similar explanation would seem satisfactory for the abdominal pain. In the latter, usually the clinical diagnosis of "surgical abdomen" is made, and an abdominal operation is performed.

The patient whose case is reported here had severe pain, especially in the left side of the chest and between the shoulders. The microscopic examination demonstrated a marked decrease in the size of the lumens of the second, third, fourth, and sixth left intercostal arteries, and it seems probable that thoracic pain in this patient was due to interference with the blood supply. The segmental distribution of the intercostal vessels to the spinal cord offers a satisfactory explanation for pain limited to certain regions or for paralysis of a particular part.

TOTAL PERSISTENCE OF THE RIGHT AORTIC ARCH. A. ARKIN.

The complete report is published in Wien. Arch. f. inn. Med. **12**:385, 1926.

A HUGE CONGENITALLY CYSTIC LIVER AND CYSTIC KIDNEYS. EARL O. LATIMER.
(From the Norman Bridge Pathological Laboratory of the Rush Medical College of the University of Chicago and the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago.)

Congenital cysts, although not common, are met often enough clinically to be considered in the diagnosis of tumors of the liver. They have been a pathologic curiosity for many years because of the size of the liver, the theories of origin and other features. Congenital cysts of the kidneys are far more common.

The first theory as to the origin of cysts of the liver of this type seems to have been advanced by Förster (cited by Moschcowitz to be referred to presently), who thought they were dilated bile ducts. He believed that the bile ducts had become occluded by an inflammation and as a result had become dilated because of retained bile. Among others sharing similar views are Cornil and Ranvier (Pathological Histology, trans. by Shakespeare and Simes, Philadelphia, 1880, p. 565), Forbes (*St. Bartholomew's Hosp. Rep.* **33**:181, 1897) and Blackburn (*Tr. Path. Soc. London* **55**:203, 1904).

Sabourin (*Arch. de physiol. norm. et path.* **10**:62 and 213, 1882) carefully studied two cystic livers and in one found cirrhosis; therefore he concluded that the cysts were caused by the cirrhosis. He believed that they were new epithelial growths, formed from newly formed bile ducts and called them "angioma biliare."

Siegmund (*Virchow's Arch. f. path. Anat.* **115**:155, 1889) objected to the inflammatory theory, and suggested that they are true cystadenomas. However, he did not state whether they were formed from bile ducts or liver cords. Hippel (*Virchow's Arch. f. path. Anat.* **123**:473, 1891), speaks of cystadenomas formed from bile passages that were originally present. Nauwerck and Hufschmid (*Beitr. z. path. Anat. u. z. allg. Pathol.* **12**:1, 1893), and v. Kahlden (*Beitr. z. path. Anat. u. z. allg. Pathol.* **13**:291, 1893) also called them cystadenomas, while Dmochowski and Janowski (*Beitr z. path. u. z. allg. Pathol.* **16**:102, 1894) called them fibro-adenomas. The latter workers found cystic livers in connection with cystic kidneys, and, believing that the latter were true tumors, presumed that the cysts of the liver also were true tumors.

Still (*Tr. Path. Soc. London* **49**:155, 1898) was the first to express the opinion that they had their origin in embryonal maldevelopment. Moschcowitz (*Am. J. M. Sc.* **131**:674, 1906) studied the cysts carefully and agreed with Still. Moschcowitz says, "non-parasitic cysts of the liver are associated with congenital anomalies in other parts of the body especially with cysts of the kidney. Such cysts of the liver are always associated with congenital anomalies of the liver, consisting in aberrant bile ducts, which may be extrahepatic or intrahepatic. These aberrant ducts are embryonal 'rests,' formed in the course of development of the liver, and have thus far been found only in cystic livers or livers associated with cystic kidneys. Non-parasitic cysts of the liver have their origin in these aberrant ducts and may assume two forms: one, arising from inflammatory hyperplasia of these ducts; the other, by retention of fluids in these ducts, as a result of congenital obstruction. There is no valid reason for classifying these cysts among tumors."

Borst (Borst, cited by Moschcowitz) combined the idea of a tumor with that of congenital origin. He brought forth the view that in the complicated process of embryonal development the relation of the growth of epithelium to connective tissue was disturbed. However Borst later told Meyenburg (*Beitr. z. path. u. z. allg. Pathol.* **64**:477, 1918) that he no longer placed as much stress on the adenomatous character as he formerly did. Borrmann (*Bibl. Medica* **13**:1, 1900) Müller (*Virchow's Arch. f. path. Anat.* **164**:270, 1901), and Vorpahl (*Beitr. z. path. Anat. u. z. allg. Pathol.* **53**:477, 1912), saw no adenoma changes.

Meyenburg subscribing to the double embryonal origin of the liver as expressed by Lewis (Keibel and Mall: Handb. d. Entwicklungsgesch des Menschen. Leipsig, 1911, p. 391) conceived of the cysts originating in bile passages of the first order. In the liver of a child who had congenitally cystic kidneys he found some blind bile passages of the first order that were connected with the parenchyma of the liver but not with the general biliary system. He believed that these were a preliminary stage of cysts of the liver and con-

cluded that the cysts formed because of the failure of some of these small bile ducts to establish their connection with the larger bile passages.

Lorentz (*Frankfurter Zeitschr. f. Path.* **29**:249, 1923) believes that there is a monistic origin of the primary bile passages; but agrees that the damage is done at the time there should be an embryonal reduction of the anastamoses among the bile passages. He failed to find any connection between the blind passages and the liver parenchyma.

Teuscher (*Beitr. z. path. Anat. u. z. allg. Pathol.* **75**:459, 1926) believes the cysts to be due to embryonal malformations, although, she always found openings between the cysts and the bile passages. Therefore, she does not believe their growth is due to a deficient opening; but rather, to a capacity for growth of the epithelium, the cystic development merely being one expression of a perverted tendency, widespread in the body, for the tissues of the excretory ducts to multiply at the expense of more highly differentiated glandular tissue. Sometimes this tendency rests on an anomaly in the germ plasma, suggesting an hereditary tendency for maldevelopment.

After this brief résumé of the theories of origin of congenitally cystic livers, it is the chief purpose of this report to place on record an unusually large congenitally cystic liver, the weight of which, so far as can be learned from other reports, is exceeded by only one other.

In 1906 Moschcowitz was able to collect only eighty-five undoubtedly congenitally cystic livers, all but fourteen in adults. There have been others reported since; but of all these only a few were greatly enlarged. The largest of these livers are listed according to their weights in the following table.

Greatly Enlarged Congenitally Cystic Livers (Arranged According to Their Weight)

Reported by	Liver Weight	Measurements	Kidneys	Year
Dmochowski and Janowski (Beitr. z. path. Anat. u. z. allg. Pathol. **16**:102, 1894)	10,850 Gm.	40 cm. broad 33 cm. thick 18 cm. long	Cystic	1894
Latimer*	8,806 Gm.	36.5 cm. broad 30 cm. thick 14 cm. long	Cystic	1927
Vorpahl (Beitr. z. path. Anat. u. z. allg. pathol. **53**:477, 1912)	8,181 Gm. (18 pounds)	40 cm. broad 33 cm. thick 17 cm. long	Cystic	1912
Courbis (These de Paris, 1877: cited by Forbes)	8,000 Gm.	.....	Cystic	1877
Kaufmann (Speziellen Path. Anat. Berlin **1**:609, 1911)	7,130 Gm.	.....	.....	1911
MacDonald (New York State J. Med. **8**:185, 1908)	6,350 Gm. (14 pounds)	.....	.....	1908
Rolleston (Diseases of the Liver, New York, 1912, p. 490)	6,095 Gm. (13 lb. 7 oz.)	.....	.....	1912
Meyenburg (Beitr. z. path. Anat. u. z. allg. Pathol. **64**:477, 1918)	5,870 Gm.	.....	Cystic	1918
Kaufmann (Speziellen Path. Anat. Berlin **1**:430, 1906)	5,500 Gm.	.....	.....	1906
Roberts (Am. J. M. Sc. **108**:664, 1894)	5,227 Gm. (11.5 pounds)	.....	.....	1894
Sharkey (Tr. Path. Soc. London **33**:168, 1882)	2,954 Gm. (6.5 pounds)	.....	.....	1882
Siegmund (Virchow's Arch. **115**:155, 1889)	2,610 Gm.	.....	.....	1889
Blackburn (Tr. Path. Soc. London **55**:208, 1909)	2,386 Gm. (5.25 pounds)	.....	Cystic	1904
Patterson (Brit. M. J. **2**:1316, 1891)	2,197 Gm. (4 lb. 13.5 oz.)	.....	.....	1890
Bristowe (Tr. Path. Soc. London **7**:229, 1856)	1,992 Gm. (4 lb. 6.25 oz.)	.....	.....	1856

* This report.

Bland-Sutton (*Brit. M. J.* **2**:1167, 1905) states that congenital cysts of the liver may enlarge the organ until it weighs 35 pounds (16 Kg.). However a careful review of his references fails to reveal a liver of that weight. Boyd (*Lancet* **1**:951, 1913) collected thirty-four instances of nonparasitic cysts of the liver that were treated surgically. Many of these were large single cysts, but there is no record of weights.

History.—A woman, aged 40, entered St. Luke's Hospital, July 3, 1926, in the care of Peter Clark because of a swelling of the abdomen and a feeling of stiffness and tightness in the lower thoracic and in the epigastric regions. She was able to be around, but worried about an abdominal mass which first was noticed eleven years before as a small nodule in the right nipple line just below the costal border. Shortly after the birth of her last child, three years before, this mass began to grow rapidly. When admitted to the hospital the liver was hard and nodular and extended to the umbilicus in the midline, a little lower on the right side and a little higher on the left side. The patient was not jaundiced but had soft clay-colored stools. Syphilitic hepatitis, echinococcus cyst and congenitally cystic disease of the liver were considered. On July 10, 1926, an exploratory operation was made by Peter Clark. The liver was greatly enlarged and studded with cysts, the kidneys were cystic also. A small piece of tissue, removed at the operation, was diagnosed congenitally cystic liver. The patient died on July 20, 1926.

The laboratory results were normal for the blood, the urine, and the feces except for clay-colored stools. The blood Wassermann test was negative.

Postmortem Examination (Edwin F. Hirsch).—The liver was a large multicystic mass weighing 8,806 Gm. (19.5 pounds). In its maximum dimensions it was 36.5 cm. broad, 30 cm. thick and 14 cm. long. About 90 per cent of the superior surface consisted of closely set cysts, the largest 8 cm. in diameter, the smallest several millimeters. The walls of the cysts were tensely distended with clear, faintly yellow fluid making the surfaces exceedingly nodular. On the superior surface only three irregular regions could be identified as liver parenchyma. They were about equal in size and finely mottled brown to purple. Many of the cysts were confluent and multilocular. The anterior border was irregular, and about 14 cm. to the right of the midline was a region stained with bile about 3 to 4 cm. (biopsy wound) and involving the border and inferior surface about equally. In the center of this was a torn place 1.5 by 1 cm. The tissue exposed was stained yellow-brown with bile, rough and slightly edematous. The inferior surface was like the superior except for two larger cysts placed one on each side, and immediately adjacent to the interlobar fissure, 10 by 9 by 7.5 cm., and 8.5 by 8 by 7 cm. They were opposite each other and near the anterior border. On the surfaces made by cutting, in a frontal plane from below through both lobes at once, a quantity of clear fluid escaped. About 90 per cent of these surfaces were composed of the cysts, which were confluent, multilocular and present throughout the entire substance of the liver. The parenchyma of the liver where present was red-brown and there was a moderate cloudy swelling. The lobular markings were only moderately distinct. The lining of the cysts were smooth, glistening white, with fibrous connective tissue strands in a network. The thickness of the cyst walls varied from 1 to 3 mm. irrespective of the size of the cyst.

The right kidney weighed 1,320 Gm. and was 22 by 14 by 8.5 cm. It was, like the liver, a multilocular mass, roughly cresentric in shape. About 95 per cent of the anterior surface was covered with closely-set cysts, varying in size from 2 mm. to 5.5 cm. in diameter. There was a small amount of yellow

lobulated fat on the outer surface of the pelvic region. The color of the cysts varied from amber to purple blue. The parenchyma of the kidney was gray-red and contained many pinhead-sized cysts. The posterior surface was like the anterior, except that 20 per cent of it was covered with yellow lobulated fat in a thin layer in the region of the pelvis. The kidney capsule stripped with difficulty, many superficial cysts being torn in the process, leaving the kidney substance gray-red and smooth. On the surfaces made by cutting, many cysts were opened and the contained fluid escaped; the color of this fluid varied from pale straw to chocolate, according to the color of the cyst. It was estimated that altogether this kidney contained about 2 per cent of the parenchyma of the kidney. This had a moderate cloudy swelling, and the cortical markings were lost.

The left kidney weighed 890 Gm. and was 20.5 by 11.5 by 8 cm. It was like the right kidney, except that no parenchyma was recognized. On surfaces made by cutting, the characteristics of the cysts were like those of the liver and the other kidney.

Histologic Examination.—Around the central vein of the liver, the cell columns were narrowed and the sinusoids widened and distended with blood cells in about one third of the lobules. In several other sections, this was less marked. There were two kinds of cysts: smaller ones, ranging in size from about that of the central vein to about 1 mm. in diameter and having a wall made up of several layers of fibrous tissue only; larger ones, ranging in size from that of the central vein (of which there were only a few) to 5 to 6 mm. in diameter (of which there were many), and having a fibrous tissue wall which was lined by a single layer of cuboidal epithelium making up about one fifth of the thickness of the wall. All contained a homogeneous coagulum. The larger cysts were irregularly placed, the smaller were uniformly in the region of the portal triad. The smaller kind of cysts were surrounded by normal liver tissue, the others by a narrow zone of necrotic tissue just outside of the capsule. Altogether about thirty sections from twelve different regions were studied.

Book Reviews

A Textbook of Bacteriology. A Treatise on the Application of Bacteriology and Immunology to the Etiology, Diagnosis, Specific Therapy and Prevention of Infectious Diseases, for Students and Practitioners of Medicine and Public Health. By Hans Zinsser, M.D., with a Section on Pathogenic Protozoa by E. E. Tyzzer, A.M., M.D. Sixth edition. Rewritten, revised and reset, with 181 illustrations in the text. Price, $7.50. Pp. 1053. New York: D. Appleton & Company, 1927.

Shortly before the appearance of the previous edition of this textbook, medical bacteriology seemed to some observers to be approaching a standstill. Refinements of the traditional methods of bacteriology and immunology were expected to yield new facts and to permit useful new applications, but it was doubted whether these facts would be discoveries of capital importance. It was felt that new methods were required to solve many old problems and that new conceptions were needed to give theoretical value to the disjointed facts collected by those who practice the art of bacteriology. A vast amount of work is being done in practical tinkering with reactions whose fundamental nature is not understood, in making experiments which have little validity because of the uncontrolled and unknown factors which influence their results, and in explaining mysteries in terms of something more mysterious, though less familiar. The teacher of medical bacteriology is often confronted with the inconsequence of the lore of his subject, which is deep enough to float a few pellicles of practical procedures, but too shallow to bear a general idea of any draft. In some respects, this textbook is an illustration of the fact that the extraordinary practical utility of medical bacteriology is in part responsible for the extensive, but superficial knowledge of the subject. The subject-matter is still descriptive, and the language is still a functional terminology.

To become a science, bacteriology requires a broader biologic foundation and a more profound chemical and physical bias. Fortunately, it touches almost every field of biologic investigation. Many workers are engaged in the study of problems which have no immediate promise of becoming diagnostic tests, and in these times institutes as well as individuals are attempting to discover some of the natural laws of infection and resistance. From the old source of practical investigation, on which, in Pasteur's hands, bacteriology was founded and from general biologic sources, an accumulation of facts is now taking place with amazing rapidity. Although neither the unifying conception nor the new methods of approach are apparent, Dr. Zinsser can state fairly, as he does in his preface, that "since the last edition bacteriology and immunology have made strides out of proportion to the brief period which has elapsed."

This period is five years. Many of the recent discoveries are described at length in this book. A new chapter is given to a presentation of the recently acquired knowledge of the streptococci and their toxins in connection with scarlet fever and erysipelas. The summary of the knowledge of the bacteriophage is an excellent condensation, at the end of which the author expresses his opinion that the bacteriophage is not a living virus. The chapter on bacterial metabolism, revised by Dr. Howard Mueller, is an improvement, but does not seem to reach the goal toward which it aimed. Modern work on filterable viruses required the rewriting of the section dealing with them. While this presentation is an advance,

the section could have been improved by a more detailed discussion of filtration, by a more exact and unified treatment of the cellular inclusions so common in tissue from animals infected with these viruses, and by the omission of some diseases which have been shown to be due to other agents than the filterable viruses. A special section could have been profitably devoted to *Rickettsiae,* and in this such diseases as typhus fever would naturally find their place. Much work on bacterial variation—variation in form and in function—has been passed over with the appearance of the fixed attitude of the monomorphistic bacteriologist who arose as an indispensable guide in the days when mixed cultures were somewhat more common than they are now. Nevertheless, the author, on page 291, accepts the possibility of mutation, describes the smooth and rough variants of cultures and their different properties, and publishes on page 662 a branching swollen form of *B. subtilis,* which has been instructive to such pleomorphists as Löhnis. Throughout the book there is much evidence of the thoughtful revision which it has received.

In the revision, however, temporal adverbs have escaped correction. The word "recently" is used to refer to events occurring in 1901, 1905, 1915, 1922 and really recently. Typographical errors, which were common in previous editions, are much fewer in this. Other incomplete statements, inadequate descriptions of technical procedures and errors make up a moderately long list, but are perhaps of no great consequence, as they can be corrected by any reader except the novice. For example, some additions of tabulated figures are incorrect; the distribution of blood groups is not correctly given, and their percentages sum up to 108 per cent; the confusion between p_H and hydrogen ion concentration appears here as it does in much bacteriologic literature; the chapter dealing with the dysentery bacilli would be more valuable if it included more of the results of English investigators; the sections dealing with the bacteriologic examination of water and milk do not set forth the most recent procedures recommended by the Committee on Standard Methods. The classification and nomenclature used are based chiefly upon Migula's system published in 1897, which implies that perhaps, in the present state of ignorance, attempts such as that made in Bergey's manual, to introduce new names and new groupings are futile. A new term "brucella," however, is used for the *abortus-melitensis* group. But for some reason not explained, *B. pyocyaneus* is described under the Brucella caption.

A frank review must notice these inadequacies, which, however, do not detract greatly from the usefulness of the book. In fact, a few errors in a textbook are advantageous to the student, developing his faculty for criticism and emancipating him from the authority of the printed page. I have always found this a most useful textbook, and no edition has served its purpose so admirably as the present one.

A special feature of the book is the inclusion of clinical and public health matter in furtherance of the authors intention of "developing the book into a manual of infectious diseases." A good book on infectious diseases is urgently needed, and this volume satisfies that need in part. But to include sufficient clinical and pathologic descriptions, and adequate presentation of epidemiologic and hygienic measures in a textbook devoted to technical medical bacteriology would strain the covers of a bulkier volume than this one. The well selected material of this nature which Dr. Zinsser has placed in this book adds greatly to its value as an aid to the medical student, the practitioner and the specialist in this field.

The section on the difficult subject of mycology, with special reference to the pathogenic yeasts, molds and so-called "higher bacteria" is written by Prof. J. G.

Hopkins, who has enlarged and improved his original chapters. Although the knowledge in this field does not lend itself to categorical statement, it has been well and usefully arranged by the author.

A new section on pathogenic protozoa is contributed to the volume by Professor Tyzzer. This is a brilliant summary of the essential and well established knowledge of these organisms. It is questionable, however, whether protozoology should be included in a textbook on bacteriology. Such an association inevitably limits the space which can be given to the consideration of protozoa. Its inclusion indicates that the term bacteriology, which has already been stretched over immunology and serology, is being further extended to cover all those fields of microbiology which relate to the parasitism of man and animals by lower organisms. It indicates, in fact, a need for a course or treatise on parasitism in general, including not only bacteria and protozoa, but also the helminths, arthropods and all types of parasites, together with the pertinent phases of medical entomology.

Any adverse comments on this book by the reviewer, who is a grateful pupil of Dr. Zinsser, are selected from a general field of admiration for the comprehensiveness and utility of this textbook. It is an interesting, readable, stimulating and accessible reference book, a guide and aid to all who deal with the cause, prevention and cure of infectious diseases.

In the change in the size of the page, in the clear printing on thin paper and in the general composition of the book, the publishers have exhibited their usual fine craftsmanship. Some of the illustrations are disappointing, for reasons not attributable altogether to the publisher. The new figures, however, illustrating the section on protozoology are especially well produced.

DIE BIOLOGIE DER PERSON. EIN HANDBUCH DER ALLGEMEINEN UND SPEZIELLEN KONSTITUTIONSLEHRE, HERAUSGEGEBEN VON PROF. DR. T. BRUGSCH UND PROF. DR. F. H. LEWY. Volume 1. Berlin and Vienna, Urban & Schwarzenberg, 1926.

The study of human constitution is a relatively young branch of medical science. Although traces of it can be found in all periods of medical history. it is not until the last decade of the nineteenth century that special attention was given to the individual and his relation to diseases. Brugsch sees in the development of our knowledge of human constitution a reaction against the one-sided etiologic conception of diseases that followed the great discoveries of Pasteur and Koch. The new branch of medicine has received its most important stimulation from clinical observation, as well as from the study of heredity. The progress in endocrinology and roentgen-ray diagnosis also is of great importance. According to Brugsch, the year of the beginning of the World War, 1914, is a turning point in the history of human constitution. The call to arms of hundreds of thousands of the best men of the nations gave the possibility for systematic studies on young and healthy persons. Thus, the study of the constitution gradually developed into the biology of the individual.

It is remarkable that in this short period of time so much material has accumulated that a system on human biology has been started that will fill four volumes, the first of which has recently been published. The work has been divided among writers whose names are familiar to those interested in questions of heredity and constitution.

The first volume contains a brief introduction to the study of the human constitution and the individual, written by Brugsch. It is followed by a chapter on the problems of individuality, in which E. Strauss discusses the different theories, especially those expressed by the great German natural philosophers

from Kant to Driesch. H. Salinger explains the mathematical evalution of statistical observations, and his clear definition will be of great help to those who want to find their way in this intricate field. I. Kaup emphasizes the importance of the normal in its relations to the individual. The norm is usually determined by the arithmetical mean. Rautmann, starting from the Latin word "norma-rule," says that everything which occurs most frequently should be called normal. It will be of interest to the pathologist to learn that the size and the weight of the organs are little influenced by the normal variations in the length of the body.

Much space, of course, is given to heredity. J. W. Johannsen's part deals with the general problems of genetics, while G. Just gives an excellent presentation of its special fields. Studies of human beings are much more difficult than those of animals and plants. But from the numerous genealogic trees of various malformations and diseases known to occur in families, it is evident that the physician can do much in increasing the knowledge on human heredity.

Individual anatomy is the title of a chapter written by W. Lubosch. Individual anatomy deals with the description and the consideration of those properties of the body by the combination of which the anatomic constitution of a person is determined. Cooperative work in the dissecting room is essential in order to develop further this special field of anatomic research. Exact observations can also be carried out on the bodies used for teaching purposes, provided competent supervision directs the work of the inexperienced student. A summary of the most common variations in men with reference to the literature are of value to the pathologist.

G. Mittasch divides the part on pathology and diseases of the individual into the pathologic conditions during the different periods of life, the pathologic conditions of the sexes, disturbances in development, neoplasms and general disturbances of the metabolism. Certain pathologic conditions of middle age, so to say, are normal, while each age has its peculiarities in the reactions to the various alterations. F. Schiff discusses the relations between the individual and infection. From the time of Pettenkofer's experiments with cholera vibrios on himself and his associates to the recent observations on the artificial infections with malaria and relapsing fever in the treatment of general paralysis, an enormous amount of material has accumulated to show the importance of the individual in susceptibility and course of infections. Naturally, the individuality of the infecting agent also has to be taken into consideration. As each age has its own anatomic, physiologic and pathologic conditions, it also has its own reactions against infections. Schiff analyzes the morbidity and mortality of the different infectious diseases according to age and sex.

B. Lebzelter takes up the question of constitution as related to the various races. The marks of distinction that are commonly used in classifying the human races are: length of the body, complexion and shape of the skull, face and nose. Lebzelter also refers to the differences in the blood groups and in the blood picture. His remarks on the influence of endemic diseases on the constitution of persons of various races deserve special attention. Many factors believed to be signs of racial inferiority are perhaps only the results of diseases from which a given race has been suffering for many generations. Special chapters are devoted to the formation and extinction of types and to the reaction of the races to diseases.

The last part of the book gives an account of the duration of life in man. H. Uhlmann speaks of the duration of life in the past centuries and in the last decades, of the individual duration of life among various races, taking into consideration internal and external conditions and social differences.

This brief review gives an idea of the large amount of material that has been accumulated in this first volume of over 1,000 pages. Not all the parts are of the same value, as is always the case when a book has been written by many different authors; but, the physician, and especially the pathologist, will find that the book, as a whole, contains much valuable information in regard to subjects of great interest. If the future volumes maintain the promise of this volume, the system on the biology of the individual can be recommended highly.

The book is well printed, but the paper used is of slightly yellow color, which makes the reading a little fatiguing. A complete and comprehensive index is attached to the first volume.

MUSCULAR CONTRACTION AND THE REFLEX CONTROL OF MOVEMENT. By J. F. FULTON, B.Sc. (HARVARD), M.A., PH.D. (Oxon). Price, $10. Pp. 664. Baltimore: Williams & Wilkins Company, 1926.

Only a special student of this subject could venture to write critically of this book, and it is with the assurance that competent critics are at work on reviews that a general impression is offered here.

It is a large book recounting in detail the extraordinarily persistent and ingenious efforts of a great many men to unravel the complexities of the anatomic structure of muscles, of the relations of nerves to them, and of the central nervous system, so far as it is concerned with muscular activity. This unraveling has been attempted in part directly, but conclusions have been drawn especially from the results of experiments so varied as to allow these relations to be tested. The response of muscles constitutes the most clear-cut and easily measured criterion of the activities of the nervous system, and this may explain the great amount of attention devoted to this subject by the best minds interested in physiology. If this were not considered, it might seem that an excessive amount of effort has been expended on the study of this function since there is so much ignorance concerning most of the other functions that have a much greater bearing on human happiness. One is astounded by the extent of information in this field, it is not even expressed in ordinary language, and any one not accustomed to this language must give the most strained attention to grasp the meaning. But the subject seems to be extremely well reviewed in this book, and apparently a great deal of knowledge has been contributed by the author.

It is particularly pleasant to read a review of the history of all those who have studied muscular contraction by one who, as may be gathered from internal evidence alone, is enthusiastic about the history of medicine. The other chapters are as concise and clear as possible, and one is greatly aided by the discussion and careful summary at the each of each chapter. But practically every chapter reveals the gaps that remain in our knowledge of the most fundamental elements of muscular activity and of nervous control; to the reader the nature of the cerebellum is, if possible, more obscure than it used to be, and the study of this organ will at least maintain the interest for a long time. In the meantime this book should not only be the most instructive one to read but the most useful for reference.

THE NATURAL PROCESSES OF HEALING IN PULMONARY TUBERCULOSIS. By MARC JAQUEROD, M.D., Physician in charge, Grand Hotel Sanatorium, Leysin, Switzerland, Medical Director of the "Societé Climáterique de Leysin." Translated by J. D. Sinclair. Pp. 117, with 60 X-Ray illustrations and 45 diagrams. New York: William Wood & Co., 1927.

After a brief and somewhat apodictic introduction to the elements of the pathologic anatomy of tuberculosis, the different modes of healing in pulmonary tuberculosis are discussed. This discussion dwells much on the surface of the

phenomena and does not take advantage of the more profound studies along similar lines that have been developed during recent years. Particular emphasis is given to healing by resolution, which is, undoubtedly, a significant and the most satisfying way of healing. But this process, the significance of which has long been overlooked, is not as novel a concept as would appear from the author's text; it has been extensively discussed during the last few years, on the basis of both experimental and clinical-roentgenologic observations, notably by American and German workers. Nevertheless, the instructive roentgenograms and clear diagrams given in the book are a valuable addition to the still scanty evidence on natural processes of healing. The pathologist will be particularly stimulated by this study, since his contribution to this phase of tuberculosis is extremely small; and there are many open questions to be decided by the cooperation with the morphologist, as indicated by Dr. Jaquerod. In the future it will be necessary to study whether resolution is chiefly effected by the expectoration of the exudate, as stated by the author, or whether resorption is a more important factor. In patients whose roentgen-ray records show a clearing of an infiltrative process in the lung the pathologist will have to decide whether the clearing from the anatomic point of view is as complete as the roentgenogram frequently indicates. The reproductions are well executed; the translation could have been more careful.

THE CLINICAL INTERPRETATION OF BLOOD CHEMISTRY. By ROBERT A. KILDUFFE. Price, $2.50. Pages 186. Philadelphia: Lea and Febiger, 1927.

As the title announces, this volume is concerned only with the interpretation of the laboratory observations in the chemical analysis of the blood. No methods are given, and no discussion of the relative value of methods is attempted. It is well nigh impossible for the physician to become familiar with the technicalities of the numerous chemical analyses of the blood that are so necessary in arriving at a correct diagnosis or at a correct idea of how the patient is progressing. He must be familiar, however, with the interpretation of all the data; these are not always easily available. There is, accordingly, a need for a book of this kind.

The normal and pathologic variations in the nonprotein nitrogen, urea, uric acid, creatinine, cholesterol, sugar, calcium, phosphorus, chloride, ammonia and proteins of the blood are comprehensively considered. There is also a discussion of blood sugar in diabetes, of the glucose tolerance test, of the dietetic management of metabolic conditions and of the calculation of a diabetic diet particularly with relation to the administration of insulin. All this necessarily involves a discussion of acidosis, acid base balance and hydrogen ion concentration.

The data and explanations in this volume are dependable. The writer's style is simple and direct. Many subjects difficult to understand are thus made easy of comprehension. For this reason, the reviewer believes the book is well worth while and finds a place already made for itself.